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Ilo Marie Grundberg, Janice Gray v. The Upjohn Company : Brief of Appellant

Utah Supreme Court

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IN THE SUPREME COURT OF THE STATE OF UTAH

ILO MARIE GRUNDBERG, and JANICE GRAY, and the estate of Mildred Lucille Coats.	U.S. Dist. Crt. No. 89-C-274-W
Respondents,	
vs.	Utah Supreme Court No. 900573
THE UPJOHN COMPANY,	Priority No. 12
Petitioner.	

APPENDIX TO BRIEF OF PETITIONER THE UPJOHN COMPANY ON CERTIFIED QUESTIONS

VOLUME II

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cosponsor of Senate Joint Resolution 330, and his colleagues on the Senate Judiciary Committee. It was through their special effort that the bill was reported out of that committee for full Senate consideration. I would also like to express my appreciation to the other 31 cosponsors of the bill for their support.

It was on June 28, 1984, that I introduced Senate Joint Resolution 330 on behalf of nearly 1.5 million Americans who have a condition that is relatively unknown. Approximately 125,000 people join their ranks each year. These individuals are ostomates. They have in common an "ostomy," a type of surgery required when a person has lost the normal function of the bowel or bladder, due to birth defect, disease, injury, or other disorder. Such operations include colostomy, ileostomy, and urostomy. Ostomates are of all ages, and represent every race, occupation, and ethnic background. They do return to normal living and community responsibility, but not without first overcoming the trauma associated with this radical surgery.

Public awareness and education efforts can help. Mutual aid and support groups can also be of great assistance to ostomates and their families. The first local ostomy association was formed in 1949, and in 1962 the United Ostomy Association was established. This association, with over 625 chapters—three in the State of Hawaii—and international affiliation, is dedicated to helping every ostomy patient return to normal living through mutual support, education in proper ostomy care, exchange of ideas, assistance in improving ostomy equipment and supplies, advancement of knowledge of gastrointestinal diseases, and public education about ostomy.

The Visiting Program is the most important activity of the United Ostomy Association. The volunteer members of local chapters, composed primarily of ostomates, provide preoperative preparation and support as well as postsurgical followthrough on a person-to-person basis. These trained and certified members are carefully selected to visit a new patient in the hospital or at their home, upon request and with the consent of the surgeon. As one member of a team whose task is to return the patient to health and activity, the visitor provides help which cannot be duplicated. To a new patient, a successful ostomate symbolizes good outcome.

At regular monthly meetings, open to anyone who is interested, members can exchange practical and personal experiences, see ostomy equipment displayed, and hear speakers. Through the Visiting Program and chapter meetings, thousands of people have returned to active and productive lives by adjusting to their new way of life.

Without greater public understanding of this type of surgery, the fear of those about to undergo the surgery and of family members and loved ones who are so important to the rehabilitation process tends to increase. For the reasons I have stated, together with Senator GRASSLEY and other concerned cosponsors of the measure, I urge the adoption of Senate Joint Resolution 330.

Mr. GRASSLEY. Mr. President, today we are considering a resolution, which has already passed in the House of Representatives, designating this month, August 1984, as "Ostomy Awareness Month"; 1.5 million people have undergone an ostomy due to the loss of the normal function of their bowel or bladder. Fortunately, all of these people are able to resume their previous lifestyles after the surgery.

The United Ostomy Association has 50,000 members whom the association counsels through the trauma of surgery and the readjustment that is necessary after surgery. Not only does the association help ostomates, but they also assist the families and friends in gaining understanding and support for their friend or family member.

Many well-known people have had one of the three types of ostomies, a colostomy, an urostomy or an ileostomy, and have become spokespersons for ostomates. We can do our part too by designating this month as "Ostomy Awareness Month" and thereby promoting the education of the American population and commending the people who have had an ostomy and continue to live as they had before the surgery. I urge you to support this important resolution.

The PRESIDING OFFICER. The joint resolution is open to amendment. If there be no amendment to be proposed, the question is on the engrossment and the third reading of the joint resolution.

The joint resolution was ordered to be engrossed for a third reading and was read the third time.

Mr. BAKER. Mr. President, I ask unanimous consent that the pending measure be laid aside and the Senate turn to the consideration of House Joint Resolution 587, Calendar Order No. 1132.

The PRESIDING OFFICER. The joint resolution will be stated by title.

The assistant legislative clerk read as follows:

A joint resolution (H.J. Res. 587) designating the month of August 1984 as "Ostomy Awareness Month."

There being no objection, the Senate proceeded to the consideration of the joint resolution.

Mr. MATSUNAGA. Mr. President, inasmuch as the language of the House joint resolution is exactly the same as that of the Senate Joint Resolution 330, I rise in full support of the measure and ask for its immediate passage.

The PRESIDING OFFICER. The joint resolution is before the Senate and open to amendment. If there be no amendment to be offered, the question is on the third reading and passage of the joint resolution.

The joint resolution (H.J. Res. 587) was ordered to a third reading, was read the third time, and passed.

The preamble was agreed to.

Mr. BAKER. Mr. President, I move to reconsider the vote by which the joint resolution was passed.

Mr. MATSUNAGA. Mr. President, I move to lay that motion on the table.

The motion to lay on the table was agreed to.

Mr. BAKER. Mr. President, I ask unanimous consent that Senate Joint Resolution 330 be indefinitely postponed.

The PRESIDING OFFICER. Without objection, it is so ordered.

FEDERAL FOOD, DRUG, AND COSMETIC ACT AMENDMENT

Mr. BAKER. Mr. President, could I inquire next of the minority leader if it is possible for him to clear for action by unanimous consent Calendar Order No. 1115, S. 2926, the drug bill.

Mr. METZENBAUM. Mr. President, reserving the right to object, and I shall not object, I wish to address myself for one moment to the minority leader.

Mr. BAKER. Mr. President, I am advised now that it may take a few additional moments to get that in shape.

I withdraw my request of the minority leader.

Mr. President, I believe now that the earlier matter may be cleared.

Let me renew my inquiry of the minority leader.

I wish now to go to Calendar No. 1115, S. 2926, if the minority leader can clear that.

Mr. BYRD. Mr. President, the matter has been cleared on this side, and there is no objection.

Mr. BAKER. I thank the minority leader.

Mr. President, I ask the Chair to lay before the Senate Calendar Order No. 1115, S. 2926.

The PRESIDING OFFICER. The bill will be stated by title.

The assistant legislative clerk read as follows:

A bill (S. 2926) to amend the Federal Food, Drug, and Cosmetic Act to revise the procedures for new drug applications, to amend title 35, United States Code, to authorize the extention of the patents for certain regulated products, and for other purposes.

There being no objection, the Senate proceeded to consider the bill.

Mr. HATCH. Mr. President, we have before us the most important pharmaceutical legislation to come before Congress in many years. This bill, S. 2926, is the final version of S. 2748, the Drug Price Competition and Patent Term Restoration Act of 1984. This is a groundbreaking compromise in the public interest. It reconciles the opposing, competitive interests of two segments of the pharmaceutical industry which have often stymied each other's attempts to improve the law. The research-based drug industry ob-

tains an extension of patents for new drug discoveries to compensate them for the time spent off-market in Food and Drug Administration review. The generic drug industry gets the ability to bring generic copies of off-patent drugs to market as soon as the patent expires, without the needless reduplication of studies and tests already in FDA's files.

The public receives the best of both worlds—cheaper drugs today and better drugs tomorow. The proliferation of new generics for some of the most important drugs on the market will save consumers an estimated $1 billion or more over the next decade. The added patent life will restore to our domestic drug companies some of the incentive for innovation which has weakened as Federal pre-market approval requirements have become more expensive and time-consuming. That incentive will produce both the investment and commitment to reseach and development that will again place the United States in unquestioned leadership in the field. And it will generate an increase in the number of important new drugs, among the most vital causes for this century's dramatic increase in the length and quality of life.

Now, those who have been following this bill know this is a vastly simplified account of the bill and its effect. It is involved and is carefully balanced at a number of points in ways only lawyers could have devised. But it is a good bill, one which I have heartily endorsed and promoted in the Senate. It is backed by a wide range of organizations including the Pharmaceutical Manufacturers' Association, the AFL-CIO and numerous individual unions, the American Association of Retired Persons, and the National Council of Senior Citizens.

As you are probably also aware, several research-based pharmaceutical companies have felt that the compromise embodied in S. 2748 was not adequate and have pressed for changes in the bill. During the past 3 months I have met with many of these companies to discuss their concerns as has Congressman HENRY WAXMAN, the bill's House sponsor, and indeed as have many members of my committee. While I believe S. 2748 enjoys overwhelming support in the Senate, it has certainly been my belief that it is preferable to accommodate requests for changes which do not disturb balances essential to the bill.

As the time remaining during this session has decreased, discussions over these concerns have intensified. Hoping that I could catalyze a final agreement among the interested parties, we met Tuesday and Wednesday and conducted many hours of intense negotiation. We discussed and placed on the table issues relating both to the abbreviated new drug application (ANDA) and patent portions of the bill.

Further negotiations ensued yesterday with Congressman WAXMAN, the House sponsor, in an attempt to develop a final position which would be satisfactory to everyone. I am pleased to report that these negotiations bore fruit and that a compromise set of amendments has been incorporated into this new bill and into the technical amendment I am proposing today. The bill, S. 2926, as amended has drawn the support of almost all of the companies opposing S. 2748, and has been accepted by Congressman WAXMAN and by the administration.

Before continuing my remarks, let me acknowledge the good offices of the many people who assisted in these negotiations, especially Mr. Joe Williams, president of Warner-Lambert and chairman of the Pharmaceutical Manufacturers Association; Mr. Jack Stafford, chief executive officer of American Home Products; Mr. Bill Haddad, president of the Generic Pharmaceutical Industry Association; Mr. William Greif, vice president of Bristol Myers; and Mr. William Ryan assistant general counsel of Johnson & Johnson. Above all, I express my appreciation for the flexibility and leadership of Chairman WAXMAN. We have enjoyed a close and amicable working relationship during the progress of this legislation through the Congress.

The elements of the compromise are:

There is to be a prospective 5-year waiting period for filing of ANDA's following approval by FDA of a new chemical entity new drug application [NDA]. For all other NDA's involving new clinical tests, there will be a 3-year period during which no ANDA approval may be made effective. This protects products whose development has taken much time and money in FDA testing and review, but which have little for no patent life left when they are finally allowed on the market.

Further, the 10-year ANDA moratorium for products approved between January 1, 1982, and the date of enactment is supplemented by a similar provision for 2 years for non-new-chemical-entity drugs.

The period of time during which an abbreviated new drug application is not to be made effective, during the pendency of a patent challenge under the statute, is extended from 18 to 30 months from the date of submission of an ANDA application containing bioequivalency data. This increases the likelihood that the litigation will be concluded within the time period during which ANDA's are not allowed.

Some of the complicated current restrictions on the nature of patents which can be extended are removed, with the provision that one patent on a product, not necessarily the first, can be extended but that total exclusive market life of the product cannot exceed 14 years.

The authority of the Secretary of Health and Human Services to deny a petition for filing an ANDA for a product not exactly similar to the original drug will be expanded to include cases where the proposed generic is a combination drug, one of whose active ingredients is different from those of the original combination drug. This will make sure that FDA retains the authority to prevent drugs from coming to market without proper tests to establish the unforeseen interactions that substituted active ingredients may have on each other.

The concern was raised that FDA might be forced under the bill to approve an ANDA, even if FDA had started proceedings to remove the original drug from the market but had not completed the process. Language was adopted which would remedy this loophole.

The treatment of animal drugs contained in S. 2748 is deleted in this bill.

I would also like to address a comment to one issue which arose during the discussion of the bill. The Patent Commissioner has expressed concern that he is required to verify the contents of applications for patent extension. This was not intended, and a wording change in the bill clarifies that he may rely wholly on the required information as represented by the applicant.

Mr. President, the United States waits for this bill.

Mr. THURMOND. Mr. President, I express my strong endorsement of S. 2926, the Drug Price Competition and Patent Term Restoration Act of 1984. This important compromise measure builds upon legislation which was reported by the Judiciary Committee and passed by the Senate in the 97th Congress. I was a cosponsor of that bill and its successors, and I am pleased to join the distinguished chairman of the Labor and Human Resources Committee, Senator ORRIN HATCH, in cosponsoring this measure.

Mr. President, patent term restoration makes eminently good sense and is fair to business and consumers alike. It encourages inventiveness by making the patent term a real and useful one. This bill adds an additional feature relating to approval procedures for drugs coming off patent, which will expedite the availability of generic drugs. This is a balanced package which addresses legitimate needs in a reasonable manner.

Mr. President, after a long delay, we are finally able to bring this important legislation before the Senate. I want to commend Senator HATCH for his persistence in this matter. I also want to express my congratulations to representatives of the various interested groups who worked together to resolve their differences so that the public interest would be served. Although, as with any compromise, everyone did not get everything that he wanted, this package represents a fair balance of interests.

I urge my colleagues to support S. 2926 so that we can enact patent term

restoration and ANDA provisions without further delay.

AMENDMENT NO. 3707

(Purpose: To make certain technical changes to the bills)

Mr. HATCH. Mr. President, I now send to the desk a technical amendment to S. 2926 on behalf of myself and the other cosponsors and Senator METZENBAUM.

The PRESIDING OFFICER. The amendment will be stated.

The legislative clerk read as follows:

The Senator from Utah [Mr. HATCH], for himself and Mr. METZENBAUM, Mr. DECONCINI, Mrs. HAWKINS, Mr. KENNEDY, Mr. DENTON, and Mr. THURMOND proposes amendment numbered 3707.

Mr. HATCH. Mr. President, I ask unanimous consent that reading of the amendment be dispensed with.

The PRESIDING OFFICER. Without objection, it is so ordered.

The amendment is as follows:

Clause (iii) of section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act, as added by section 101(a) of the bill, is amended by striking out "(or supplement to an application)" and "(or supplement thereto)", and by inserting after "approved under subsection (b)" the following "and which contains reports of new clinical investigations (other than bioavailability studies) sponsored by the applicant".

Clause (iv) of section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act, as added by section 101(a) of the bill, redesignated as clause (v), and the following new clause (iv) is inserted immediately after clause (iii):

"(iv) If a supplement to an application approved under subsection (b) includes reports of new clinical investigations (other than bioavailability studies) sponsored by the applicant and is approved after the date of enactment of this subsection, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which such supplement was submitted effective before the expiration of three years from the date of the approval of the supplement under subsection (b).

Clause (iii) of section 505(c)(3)(D) of the Federal Food, Drug, and Cosmetic Act, as added by section 101(b) of the bill, is amended by striking out "(or supplement to an application)" and "(or supplement thereto)" and by inserting after "approved under subsection (b)" the following "and which contains reports of new clinical investigations (other than bioavailability studies) sponsored by the applicant".

Clause (iv) of section 505(c)(3)(D) of the Federal Food, Drug, and Cosmetic Act, as added by section 101(b) of the bill, is redesignated as clause (v), and the following new clause (iv) is inserted immediately after clause (iii);

"(iv) If a supplement to an application approved under subsection (b) includes reports of new clincial investigations (other than bioavailability studies) sponsored by the applicant and is approved after the date of enactment of this subsection, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which such supplement was submitted effective before the expiration of three years from the date of the approval of the supplement under subsection (b).

Subsection (1) of section 505 of the Federal Food, Drug, and Cosmetic Act, as added by section 104 of the bill, is amended by striking out, beginning with ", including", all matter through "financial information".

Mr. HATCH. Mr. President, the amendment clarifies the data release provision and the 3-year moratorium for ANDA's [Abbreviated New Drug Applications]. It would protect only those new drug applications which involve new clinical investigations.

The effect on changes to existing NDA's would be to restrict coverage to only those alterations, like some changes in strength, indications, and so forth, which require considerable time and expense in FDA required clinical testing.

Mr. President, I move that the amendment be adopted.

The PRESIDING OFFICER. If there be no further debate, the question is on agreeing to the amendment of the Senator from Utah.

The amendment (No. 3707) was agreed to.

Mr. HATCH. Mr. President, I move to reconsider the vote by which the amendment was agreed to.

Mr. BAKER. Mr. President, I move to lay that motion on the table.

The motion to lay on the table was agreed to.

AMENDMENT NO. 3708

Mr. HATCH. Mr. President, at this time, I submit an amendment on behalf of Senator THURMOND and ask for its immediate consideration.

The PRESIDING OFFICER. The amendment will be stated.

The legislative clerk read as follows:

The Senator from Utah [Mr. HATCH] for Mr. THURMOND proposes an amendment numbered 3708.

Mr. HATCH. Mr. President, I ask unanimous consent that the reading of the amendment be dispensed with.

The PRESIDING OFFICER. Without objection, it is so ordered.

The amendment is as follows:

At the end of the bill insert the following new title:

TITLE —

SEC. —. (a) Title 35 of the United States Code is amended by adding immediately following section 155 the following new section:

"§ 155A. Patent extension.

"(a) Notwithstanding section 154 of this title, the term of any patent which encompasses within its scope a composition of matter which is a new drug product, if such new drug product is subject to the labeling requirements for oral hypoglycemic drugs of the sulfonylurea class as promulgated by the Food and Drug Administration in its final rule on March 22, 1984 (FR Doc. 84-9640) and was approved by the Food and Drug Administration for marketing after promulgation of such final rule and prior to the date of enactment of this law, shall be extended until April 21, 1992.

"(b) The patentee or licensee or authorized representative of any patent described in such subsection (a) shall, within ninety days after the date of enactment of such subsection, notify the Commissioner of Patents and Trademarks of the number of any patent so extended. On receipt of such notice, the Commissioner shall confirm such extension by placing a notice thereof in the official file of such patent and publishing an appropriate notice of such extension in the Official Gazette of the Patent and Trademark Office.".

(b) The table of sections for chapter 14 of title 35, United States Code is amended by adding after the item relating to section 155 the following new item:

"155A. Patent extension.".

Section 25(a) of the bill, as redesignated, is amended by striking out "9 and 10" and inserting in lieu thereof "9, 10, and 24".

Mr. HATCH. Mr. President, I would like to share with my colleagues a statement by Senator THURMOND on this amendment.

This amendment passed the Senate without objection on June 29 as an amendment to S. 1538. It would provide limited patent extension for certain oral diabetic drugs. Such relief is necessary because the FDA unduly delayed final approval for these drugs while it developed class labeling. This would restore some of the patent life lost because of the government's undue delay.

Mr. President, it is my understanding that Members of the House are willing to take this amendment, as well, so we are adding it to this bill.

Mr. METZENBAUM. Will the manger of the bill be good enough just to repeat what this amendment is? This is not the Thurmond textile amendment?

Mr. HATCH. Mr. President, this has nothing to do with textiles. This is an amendment that provides limited patent extensions for certain oral diabetic drugs. Such relief is necessary because the Food and Drug Administration unduly delayed final approval for these drugs while it developed class labeling. This would restore some of the patent life lost because of the Government's undue delay.

Mr. METZENBAUM. Mr. President, I have to say to my colleague from Utah that this amendment is not agreeable at all. I have not heard of this amendment before. This is the first time I have heard about a patent extension with respect to diabetic drugs. We have many patent extensions proposed.

Mr. HATCH. Mr. President, if the Senator will yield for just a moment.

Mr. METZENBAUM. Mr. President, I have to advise my colleague that although apparently one of my staff members saw fit to clear it, it does not reflect my views. But if he did so, I am not going to renege on that understanding. I withdraw my objection.

Mr. HATCH. I appreciate the distinguished Senator from Ohio doing that.

I might add that this is part of the package that has been considered and accepted by, I believe, Representatives in the House and the Senate. I understood that it had been cleared. I appreciate that kindness on the part of the distinguished Senator from Ohio.

Mr. METZENBAUM. Is the Senator finished with the amendment?

Mr. HATCH. I have not moved the amendment yet.

Mr. METZENBAUM. I would like to be heard on the bill when the Senator from Utah is finished.

Mr. HATCH. I am not quite through yet.

Mr. President, I move the amendment.

The PRESIDING OFFICER. Is there further debate on the amendment? If not, the question is on agreeing to the amendment of the Senator from Utah [Mr. HATCH].

The amendment (No. 3708) was agreed to.

Mr. HATCH. Mr. President, I move to reconsider the vote by which the amendment was agreed to.

Mr. BAKER. I move to lay that motion on the table.

The motion to lay on the table was agreed to.

Mr. HATCH. Mr. President, I yield the floor to the distinguished Senator from Ohio.

Mr. METZENBAUM. Mr. President, I spent the last couple of days on this bill, and I am frank to admit that I have grave misgivings about it. I have misgivings about it because it provides the Senate with the horns of a dilemma.

One part of the bill provides a good legislative approach to the use of generic drugs, and it breaks some new ground in that area. I support the concept of the use of generic drugs. I think it helps senior citizens as well as all people in our society if you can buy drugs that are not merely by reason of their name and the advertising but based upon the content.

But there is another part of the bill that gives me great concern; that is that portion of the bill that provides for an extension of patents under various and sundry circumstances.

I have seen a proliferation of legislation in this session of Congress calling for the extension of patents. Some brilliant lawyer or lobbyist came to the conclusion that if we went to the Congress we could get patents extended beyond their usual 17-year term. So we have seen bills having to do with pharmaceuticals and chemicals, and agriculture chemicals, specific drugs, various and sundry drugs, some described rather generally, and in each instance there was a strong case made, "Well, the FDA delayed it or whatever and there should be an extension."

This bill is not specific in that respect. It provides for a more general extension of patents. In that respect, I have grave reservations about it.

Then there are provisions of this bill that provide for specific extensions. And each day of extension, it should be pointed out, costs the American consumers literally hundreds of thousands, and in some instances millions, of dollars. When I attempted to determine how much the extension rights for the patent extensions provided in this bill were worth, I was unable to get a figure. Nobody can say whether it was $1 billion, $2 billion, $5 billion, or $50 billion. I am frank to admit I do not know the amount. But I know that it is a large amount and the drug companies will clap with enthusiasm and excitement when this bill becomes law.

Then there is another provision in this bill that breaks even further more new ground, and that is it is a totally new concept. It provides that the FDA, upon approval of a drug, may grant exclusivity, exclusive rights to use that drug for 5 years. Then if you read it closely enough, you will learn it really is not 5 years, it is closer to 6 years because of the date and the manner in which it is written.

Well, that was enough and that was sufficient reason to be concerned about the passage of this legislation. But then we learned just in the last few minutes that the language of the 5-year exclusive marketing provision which the FDA can give may also, in some way, detour or detract from the right of generic drug manufacturers and perhaps others as well to challenge the patent during that period.

I have received an iron-clad assurance from the man primarily responsible for the passage of this legislation, the distinguished and well-respected Congressperson from California HENRY WAXMAN, who said if this is a problem, he will see to it that it is taken care of in the House. I want at this point to say very publicly that one of the reasons that I have withdrawn any objection to this bill is because of the distinguished record that the Congressperson from California, Congressman WAXMAN, has had and the confidence that I have in his legislative approach.

I still have reservations. I still have concerns. I will not oppose this legislation. I am not at all certain that the Senate, when it passes it this evening, will be doing the right thing, but I will not stand in the way of the passage.

There are some fine groups, generic groups, retired senior citizens groups, Congress Watch, other groups of that kind, consumer groups, who have indicated their support. I hope they are right. I hope they are not making a mistake. I hope that they have not given away too much of the ball game to the big drug manufacturers of this country, and only time will tell whether or not I am right.

On one other subject, there are many people asking what this bill is all about; what it means; how do you interpret it. Let me say, for one, that I interpret it in only one manner. Nobody can change the language of the legislation. It speaks for itself. So notwithstanding anybody who may feel that they can interpret the language of this legislation in one way or another, I want the courts to understand that the legislation speaks for itself and the interpretation which anyone may make on the floor does not really add anything to that interpretation.

Mr. HATCH. Mr. President, I cannot overstate the importance of this bill. It will revolutionize the drug industry and the drug market. It is a boon to both consumers and producers, and I know of no group which opposes it as amended.

The support is bipartisan, and it is overwhelming.

Mr. President, I cannot tell you how much the distinguished Member of Congress, Congressman WAXMAN, has done to help bring this bill about. Without his tireless, unrelenting leadership, I do not know that we would ever have had this bill. And there has been a lot of work here in the Senate, and especially in the Labor and Human Resources Committee, as well.

I was pleased to join in the effort with Congressman WAXMAN in this bipartisan effort.

I want to thank the people in industry, the consumer groups, the people in the generic pharmaceutical industry, the people in the Pharmaceutical Manufacturers Association, and all of those who have worked with us. I want to thank the Senator from Ohio. I would like to thank the distinguished Member of Congress, Congressman WAXMAN.

The PRESIDING OFFICER. The bill having been read the third time, the question is, Shall the bill pass?

The bill (S. 2926) was passed, as amended as follows:

S. 2926

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "Drug Price Competition and Patent Term Restoration Act of 1984".

TITLE I—ABBREVIATED NEW DRUG APPLICATIONS

SEC. 101. Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) is amended by redesignating subsection (j) as subsection (k) and inserting after subsection (i) the following:

"(j)(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

"(2)(A) An abbreviated application for a new drug shall contain—

"(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (6) (hereinafter in this subsection referred to as a 'listed drug');

"(ii)(I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug,

"(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

"(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active in-

product development protocol was initially submitted under section 515(f)(5) and ending on the date the protocol was declared completed under section 515(f)(6).

"(4) A period determined under any of the preceding paragraphs is subject to the following limitations:

"(A) If the patent involved was issued after the date of the enactment of this section, the period of extension determined on the basis of the regulatory review period determined under any such paragraph may not exceed five years.

"(B) If the patent involved was issued before the date of the enactment of this section and—

"(i) no request for an exemption described in paragraph (1)(B) was submitted.

"(ii) no major health or environmental effects test described in paragraph (2) was initiated and no petition for a regulation or application for registration described in such paragraph was submitted, or

"(iii) no clinical investigation described in paragraph (3) was begun or product development protocol described in such paragraph was submitted.

before such date for the approved product the period of extension determined on the basis of the regulatory review period determined under any such paragraph may not exceed five years.

"(C) If the patent involved was issued before the date of the enactment of this section and if an action described in subparagraph (b) was taken before the date of the enactment of this section with respect to the approved product and the commercial marketing or use of the product has not been approved before such date, the period of extension determined on the basis of the regulatory review period determined under such paragraph may not exceed two years.

"(h) The Commissioner may establish such fees as the Commissioner determines appropriate to cover the costs to the Office of receiving and acting upon applications under this section.".

(b) The analysis for chapter 14 of title 35 of the United States Code is amended by adding at the end thereof the following:

"156. Extension of patent term.".

SEC. 202. Section 271 of title 35, United States Code is amended by adding at the end the following:

"(e)(1) It shall not be an act of infringement to make, use, or sell a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913)) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs.

"(2) It shall be an act of infringement to submit an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act for a drug claimed in a patent or the use of which is claimed in a patent, if the purpose of such submission is to obtain approval under such Act to engage in the commerical manufacture, use, or sale of a drug claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

"(3) In any action for patent infringement brought under this section, no injunctive or other relief may be granted which would prohibit the making, using, or selling of a patented invention under the paragraph (1).

"(4) For an act of infringement described in paragraph (2)—

"(A) the court shall order the effective date of any approval of the drug involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed,

"(B) injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, or sale of an approved drug, and

"(C) damages or other monetary relief may be awarded against an infringer only if ther has been commerical manufacture, use, or sale of an approved drug.

The remedies prescribed by subparagraphs (A), (B), and (C) are the only remedies which may be granted by a court for an act of infringement described in paragraph (2), except that a court may award attorney fees under section 285.".

SEC. 203. Section 282 of title 35, United States Code, is amended by adding at the end the following: "Invalidity of the extension of a patent term or any portion thereof under section 156 of this title because of the material failure—

"(1) by the applicant for the extension, or

"(2) by the Commissioner,

to comply with the requirements of such section shall be a defense in any action involving the infringement of a patent during the period of the extension of its term and shall be pleaded. A due diligence determination under section 156(d)(2) is not subject to review in such an action.".

TITLE III—SEPARABILITY CLAUSE

SEC. 301. If any provision of this Act is declared unconstitutional, or the applicability thereof to any person or circumstances is held invalid, the constitutionality of the remainder of this Act and the applicability thereof to other persons and circumstances shall not be affected thereby.

TITLE IV—MISCELLANEOUS PATENT EXTENSIONS

SEC. 401. (a) Title 35 of the United States Code is amended by adding immediately following section 155 the following new section:

"§155A. Patent extension.

"(a) Notwithstanding section 154 of this title, the term of any patent which encompasses within its scope a composition of matter which is a new drug product, if such new drug product is subject to the labeling requirements for oral hypoglycemic drugs of the sulfonylurea class as promulgated by the Food and Drug Administration in its final rule of March 22, 1984 (FR Doc. 84-9640) and was approved by the Food and Drug Administration for marketing after promulgation of such final rule and prior to the date of enactment of this law, shall be extended until April 21, 1992.

"(b) The patentee or licensee or authorized representative of any patent described in such subsection (a) shall, within ninety days after the date of enactment of such subsection, notify the Commissioner of Patents and Trademarks of the number of any patent so extended. On receipt of such notice, the Commissioner shall confirm such extension by placing a notice thereof in the official file of such patent and publishing an appropriate notice of such extension in the Official Gazette of the Patent and Trademark Office.".

(b) The table of sections for chapter 14 of title 35, United States Code is amended by adding after the item relating to section 155 the following new item:

"155A. Patent extension.".

SEC. 402. Section 25(a) of the bill, as redesignated, is amended by striking out "9 and 10" and inserting in lieu thereof "9, 10, and 24".

Mr. METZENBAUM addressed the Chair.

The PRESIDING OFFICER. The Senator from Ohio is recognized.

Mr. METZENBAUM. Mr. President, I would like the RECORD to reflect the fact that the Senator from Ohio voted in the negative.

Mr. BAKER. Mr. President, I move to reconsider the vote by which the bill was passed.

Mr. HATCH. I move to lay that motion on the table.

The motion to lay on the table was agreed to.

Mr. DECONCINI. I would like to engage in a colloquy with my friend, Senator HATCH. I understand that S. 2926, as amended, statutorily codifies FDA's current regulation and practice with reference to standards for the release of trade secret, confidential commercial and financial information contained in NDA files, is that correct?

Mr. HATCH. Yes, the bill carries over from the existing regulation the provision that information is releasable—if other requirements are met—unless extraordinary circumstances are shown. Under current practice, which will be the practice under this bill, extraordinary circumstances are present for example when the information is trade secret or confidential commercial or financial information. As one specific example, release would not be permitted if the information has never been previously released and would support the application of a competitor for approval before a foreign regulatory agency. As another example, safety and efficacy data contained in an application that was not approved will not be released if the data retains possible commercial, competitive value. In short, the provision retains the applicability of the (b)(4) exemption under the Freedom of Information Act.

Mr. DECONCINI. That is my understanding also.

Mr. BAKER addressed the Chair.

The PRESIDING OFFICER. The majority leader is recognized.

Mr. BAKER. Mr. President, I wish to express my appreciation to the distinguished Senator from Utah for work well done. The work was long, hard, and done diligently. There were moments even as recently as 30 minutes ago when I thought it would be impossible for him to get this bill cleared for passage before we go out. But he did.

I think that is remarkable. I extend to the Senator my heartiest congratulations for doing so.

Mr. President, I thank the minority leader for his willingness to consider this matter, and the Senator from Ohio for agreeing to go forward without objection.

There is one other point, Mr. President, that I would like to make. The distinguished Senator from South Carolina [Mr. THURMOND], is not here. He is necessarily absent from the floor at this point. He had originally planned to offer a textile amendment to this bill. He feels very keenly about that. Many Members know of the

great interest he has in that, and the dedication that he has for the purposes to be served. But the Senator from South Carolina in his characteristically generous way agreed not to offer that amendment in order to facilitate the passage of this bill.

I wish to acknowledge that at the conclusion of this RECORD.

Mr. President, as well I am told that in addition to myself, the distinguished Senator from Ohio [Mr. METZENBAUM], had indicated to the President pro tempore that in his absence we would offer that amendment. We were released from the obligation. I thank the Senator for doing so.

Senator GORTON, and others, had indicated their objection. They all were withdrawn. I thank all Members for making it possible for us to proceed in this manner at this time.

Mr. HATCH addressed the Chair.

The PRESIDING OFFICER. The Senator from Utah is recognized.

Mr. HATCH. Mr. President, I would express my gratitude to the distinguished majority and minority leaders of this great body, and for the cooperation they have given to me and to other Members to try to get this bill passed this evening. It is historic. It is important.

I want to personally express my personal gratitude to both of them, and to everybody else who has worked to make this possible.

FEDERAL BOAT SAFETY ACT AMENDMENT

Mr. BAKER. Mr. President, I have discussed this with the minority leader. He is aware of the request I am about to make.

Mr. President, I ask unanimous consent that the Senate now turn to the consideration of Calendar No. 571, H.R. 2163, the Boat Safety Act, and that it be considered under the following time agreement:

That 30 minutes of total debate, to be equally divided between the chairman of the Finance committee and the ranking minority member, or their designees; that the committee reported amendment in the nature of a substitute be withdrawn; and that only one amendment be in order, to be offered by the Senator from Kansas [Mr. DOLE] and the Senator from New Jersey [Mr. BRADLEY], which is the text of the Enterprise zone amendment which was agreed to in H.R. 4170;

And that the agreement be in the usual form.

Mr. President, I further ask unanimous consent that following final passage of H.R. 2163, it be in order for the chairman of the Finance committee or his designee to amend the title of H.R. 163 appropriately.

Mr. BYRD addressed the Chair.

The PRESIDING OFFICER. The minority leader is recognized.

Mr. BYRD. Mr. President, I am sorry to have to object in regard to this matter. But we have not been able to clear such a time agreement with only the amendment by Mr. DOLE to be offered. There are Senators on this side of the aisle, I believe, who have amendments on the enterprise zone itself, and we have been attempting to clear the bill. We are trying to determine the nature of other possible amendments as well. But on behalf of the other Senators on this side of the aisle, I regrettably would have to object at this time.

The PRESIDING OFFICER. Objection is heard.

Mr. BAKER. Mr. President, I now have a list of items that I would like to take up. May I say to the minority leader that it is a considerable list, running to more than one page. Perhaps I could run through them, and he might be in a position then to tell me whether he could clear all or any part of these matters that would expedite that consideration.

I would propose, Mr. President, to indefinitely postpone Calendar Order 1117; pass Calendar No. 1118; indefinitely postponed Calendar No. 1119; Pass Calendar Nos. 1120, 1121, and 1122; to indefinitely postpone Calendar No. 1123, to pass Calendar Nos. 1124, 1125, 1126, 1127, and 1128; to indefinitely postpone Calendar No. 1129; to pass Calendar Nos. 1130, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1143, 1146, 1147, and 1148; and, finally, to pass Calendar No. 1150.

Mr. BYRD addressed the Chair.

The PRESIDING OFFICER. The minority leader is recognized.

Mr. BYRD. Mr. President, I have no objection to proceeding with the calendar orders mentioned by the distinguished majority leader.

NATIONAL SPINA BIFIDA MONTH

The joint resolution (S.J. Res. 275) to designate the month of October 1984, as "National Spina Bifida Month", was considered, ordered to be engrossed for third reading, read the third time, and passed.

The preamble was agreed to.

The joint resolution, and the preamble, are as follows:

S.J. RES. 275

Whereas spina bifida is a birth defect in the spinal column which occurs in one of every one thousand births in the United States;

Whereas spina bifida is the most common crippler of newborns, resulting when one or more bones in the back (vertebrae) fail to close completely during prenatal development;

Whereas while the cause of spina bifida is not known, it appears to be the result of multiple environmental and genetic factors;

Whereas although most of the March of Dimes and Easter Seal poster children have spina bifida, many people have not heard of the defect;

Whereas only a few cities in the United States have proper care centers and specialized professionals that can provide the most effective, aggressive treatment for children and adults with spina bifida;

Whereas an increase in the national awareness of the problem of spina bifida may stimulate the interest and concern of the American people, which may lead, in turn, to increased research and eventually to the discovery of a cure for spina bifida. Now, therefore, be it

Resolved by the Senate and House of Representatives of the United States of America in Congress assembled, That the month of October 1984 is designated "National Spina Bifida Month", and the President is authorized and requested to issue a proclamation calling upon the people of the United States to observe that month with appropriate ceremonies and activities.

MYASTHENIA GRAVIS AWARENESS WEEK

The joint resolution (S.J. Res. 295) to provide for the designation of the week of October 14, through October 20, 1984, as "Myasthenia Gravis Awareness Week", was considered, ordered to be engrossed for third reading, read the third time, and passed.

The preamble was agreed to.

The joint resolution, and the preamble, are as follows:

S.J. RES. 295

Whereas the incidence and prevalence of myasthenia gravis presents a significant health problem in the United States;

Whereas myasthenia gravis is a severe neuromuscular disorder, characterized by weakness of the voluntary muscles of the body;

Whereas an estimated one hundred thousand to two hundred thousand diagnosed, and over one hundred thousand undiagnosed, Americans of both sexes, and all races and ages, are afflicted with the disease;

Whereas the Nation faces a continuing need to support innovative research into the causes, treatment, and cure of myasthenia gravis; and

Whereas it is appropriate to focus the Nation's attention upon the problem of myasthenia gravis: Now, therefore, be it

Resolved by the Senate and House of Representatives of the United States of America in Congress assembled, That the week of October 14, through October 20, 1984, is designated as "Myasthenia Gravis Awareness Week" and the President of the United States is authorized and requested to issue a proclamation calling upon all Government agencies and the people of the United States to observe the week with appropriate programs, ceremonies and activities.

NATIONAL DIABETES MONTH

The joint resolution (S.J. Res. 299) to designate November 1984, as "National Diabetes Month," was considered, ordered to be engrossed for third reading, read the third time, and passed.

The preamble was agreed to.

The joint resolution, and the preamble, are as follows:

S.J. RES. 299

Whereas diabetes kills more than all other diseases except cancer and cardiovascular diseases;

Whereas eleven million Americans suffer from diabetes and five million seven hundred thousand of such Americans are not aware of their illness;

Whereas $10,100,000,000 annually are used for health care costs, disability pay-

Tab 38

S. HRG. 98-1102

DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT OF 1984

HEARING

BEFORE THE

COMMITTEE ON LABOR AND HUMAN RESOURCES UNITED STATES SENATE

NINETY-EIGHTH CONGRESS

SECOND SESSION

ON

S. 2748

TO AMEND THE FEDERAL FOOD, DRUG, AND COSMETIC ACT TO REVISE THE PROCEDURES FOR NEW DRUG APPLICATIONS AND TO AMEND TITLE 35, UNITED STATES CODE, TO AUTHORIZE THE EXTENSION OF THE PATENTS FOR CERTAIN REGULATED PRODUCTS, AND FOR OTHER PURPOSES

JUNE 28, 1984

Printed for the use of the Committee on Labor and Human Resources

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STATEMENTS

THURSDAY, JUNE 28, 1984

ADDITIONAL MATERIAL

Mr. ENGMAN. I don't have any vote. You have one, so you are one up on me. [General laughter.]

Senator HAWKINS. Do you consider the provision permitting the generic manufacturers to begin testing prior to the expiration of the patent a critical amendment which goes to the heart of this compromise?

Mr. ENGMAN. That was an issue that was initially put to us in January of this year, and at that time the board made a decision that that was one of the tradeoffs that we were prepared to give up to achieve other purposes of this legislation.

Senator HAWKINS. Thank you very much for your participation on this panel.

I will now call the third panel. Mr. Verne Willaman, a member of Johnson & Johnson's executive committee, accompanied by Mr. Stafford and Mr. Lerner.

The third panel consists of three witnesses for whom we have the highest regard. Mr. Verne Willaman, a member of the executive committee and Johnson & Johnson, heads all of Johnson & Johnson's pharmaceutical divisions. He will be testifying on behalf of 10 pharmaceutical companies which have identified provisions of the bill which they feel pose problems and require correction.

He will be accompanied by Mr. John Stafford, president of American Home Products, and Mr. Irwin Lerner, president and CEO of Hoffman-LaRoche.

Mr. Willaman, welcome, and please begin.

STATEMENT OF VERNE WILLAMAN, MEMBER, EXECUTIVE COMMITTEE, JOHNSON & JOHNSON, ACCOMPANIED BY JOHN R. STAFFORD, PRESIDENT, AMERICAN HOME PRODUCTS, AND IRWIN LERNER, PRESIDENT/CHIEF EXECUTIVE OFFICER, HOFFMAN-LAROCHE, INC.

Mr. WILLAMAN. Thank you, Senator Hawkins.

Thank you for the opportunity to appear before this committee to discuss S. 2748. You have already introduced the other people at the table. Let me also just begin by naming the other companies in our group: Bristol-Myers, Carter-Wallace, Merck, Norwich Eaton Pharmaceuticals—a Procter & Gamble company—Schering-Plough Corp., Squibb Corp., and Stuart Pharmaceuticals, a division of ICI Americas.

These companies have much in common. We are all committed to pharmaceutical research and development. We represent about half of the private pharmaceutical research and development investment in this country, an investment which over the years has propelled our country into the world technological leadership position.

In today's costly health care environment, prescription drugs, to quote a recent study, are the "least expensive form of medical therapy and greatly reduce health care costs" by cutting back the need for surgery and hospitalization. The medicines we discover and develop in our laboratories are absolutely essential to continued medical progress in this century and beyond. In human terms, the saving of lives and suffering is immeasurable.

Our companies have been responsible for some of the most significant pharmaceutical breakthroughs of the last several decades. We recognize that each time we begin to develop a new drug we are undertaking a multimillion-dollar investment. A large amount of our research never culminates in a marketed product because there are many uncertainties associated with medical research. On average, the cost of developing a new medicine in this country is now in the $70 to $85 million range, taking an average of 7 to 10 years and often longer to complete all the rigorous scientific protocols and secure FDA approval. Incentives provided by the patent system are the cornerstone of pharmaceutical research and development.

For many years, the patent system has not worked for our industry as it was intended. By the time new drugs are cleared by FDA, they have far less than 17 years of patent life. For example, FDA reported that of 205 drug products approved between 1962 and 1978, 51, or a quarter, had little or no patent life at the time of approval. We have long believed that this is a situation that merits remedy by the Congress, and indeed, efforts in this direction have been made in past years.

At the same time, Senator Hatch recently identified the need to resolve the question of how FDA approves generic versions of post-1962 drugs. A workable system must be established for approving these generics and for assuring their safety, effectiveness, and quality. But the legislation must not have the unintended effect of discouraging original research.

We fully support the objectives of the legislation that has been introduced. And furthermore, we would like to commend the committee for holding hearings on this important piece of legislation. The leadership on this issue, and advocacy of drug export legislation is an example of the kind of leadership necessary in the health care field. Expanding drug exports will encourage American technology and job opportunities. Unfortunately, the ANDA/patent term proposal in its current form will have the opposite effect.

Senator Hawkins, while we support the objectives of S. 2748, we are convinced that amendments are necessary. The amendments we are proposing are designed to achieve a fair balance between streamlining the generic drug approval process, while, at the same time, assuring patent protection for pioneer medicines. Efforts to stimulate research leading to important new therapies merit at least as much consideration as accelerating the approval process for generic copies.

This bill raises many difficult patent issues. Yesterday, at a hearing before a House Judiciary Subcommittee, Patent Commissioner Gerald Mossinghoff identified some of these issues. He said they pose such a major obstacle that despite his fervent support for patent term restoration for pharmaceuticals, he and the Patent Office oppose enactment of this legislation in its present form. Also at yesterday's hearing, Prof. Norman Dorsen, a recognized expert in constitutional law, noted that at least one central provision of this legislation raises serious constitutional questions. In light of this testimony, it is our view that hearings be held before the Senate Judiciary Committee.

Additionally, Commissioner Novitch testified this morning that FDA believes that additional changes need to be made to this bill.

Senator Hawkins, we do have a common constituent—the American consumer. Consumers should not only have access to safe and effective generic drugs. They also should have the lifesaving benefits of the innovative therapies discovered in our laboratories. These objectives can be achieved by addressing the concerns of the Patent Office and the FDA, which are the same concerns that we have identified.

We are concerned that this legislation, as drafted, would have the effect of reorienting FDA priorities toward approval of generic drugs and answering freedom of information inquiries rather than focusing, as it should, we believe, on important new therapies for American patients.

Our written testimony describes the specific amendments we are seeking. I would like to summarize them for you. In keeping with the committee's jurisdiction, I will focus on health and regulatory problems raised by the legislation.

Our first public health concern is that the bill, in its current form, could restrict FDA's ability to assure that all drugs are shown, before marketing, to be safe and effective. For most generic copies, FDA would be precluded from requesting information beyond the limited information specifically set forth in the bill. For these drugs, FDA has no authority to reject an application on the grounds that the copied drug has not been shown to be safe or effective.

We strongly feel that FDA should have clear authority to assure the safety and effectiveness of every drug on the market. We, therefore, favor an amendment that would make this FDA authority explicit.

Another major concern relates to the public disclosure of safety and effectiveness data contained in the new drug applications for pioneer drugs. Such data represents a huge research investment by the originating firm. This legislation, if enacted in its present form, would permit public disclosure of all safety and effectiveness data, and information about a drug as soon as it becomes eligible for an ANDA.

These proprietary data retain commercial value for the pioneering drug firm in the worldwide marketplace. They are of significant value to competitors abroad, and their release would erode the U.S. technological leadership. The data are particularly valuable in countries that do not provide adequate patent protection. We believe that this provision, unless amended, would have serious adverse effects on this Nation's pharmaceutical leadership.

Earlier this year, Senator Hatch made efforts to amend the Freedom of Information Act, and drove home the usefulness of U.S.-produced technical data. It is these same technical data that would be made available to foreign competitors under S. 2748. And, as I have already noted, the disclosure provision would add to FDA's already enormous burden under the Freedom of Information Act. It is difficult to see how the public benefits by having FDA resources diverted to giving foreign competitors valuable research information at the expense of approving drug applications.

Our next concern relates to the transition provisions in S. 2748. As drafted, it permits marketing exclusivity for 10 years only for new active ingredients first approved between January 1, 1982, and the date the bill is enacted. We believe this transition provision is too limited in scope. It does not apply to new uses for the drug, new dosage forms or innovative formulations, all of which require full new drug applications. Those innovations frequently are as important and contribute as much to public health as the active ingredients covered under the provision. Yet companies that invested in these important areas would be penalized by their exclusion from the transition provisions.

A second part of this concern relates to the 4-year period of marketing exclusivity for unpatentable active ingredients approved after the bill becomes effective. As FDA has made clear in previous testimony, this period is needed to evaluate patient experience with a new therapy in the first few years after its introduction. This experience often provides new insights into the drug's safety profile and appropriate use. As with the other transition period, this provision should be broadened to include all new drug approvals for products that are not patentable.

Senator Hawkins, we understand that concern also has been expressed about two other health-related issues. One is the many new burdens that this bill imposes on FDA which, among other things, would also involve the agency in patent matters for the first time. And Commissioner Novitch talked about that this morning. The second concern relates to the reversal of FDA's longstanding policy concerning combination drugs. We share these concerns with Dr. Novitch and urge that your committee consider them.

To conclude, Senator Hawkins, our 10 companies support the legislative objectives of S. 2748. But the problems we have raised here today and in our more detailed written comments must be resolved to afford maximum public health protection, as well as to continue research incentives for the pharmaceutical industry.

U.S. pharmaceutical companies always have been preeminent in developing and disseminating lifesaving and life-extending pharmaceutical products. But recent statistics indicate this leadership is declining. The U.S. share of world pharmaceutical research and development expenditures has fallen from more than 30 percent before 1960, to less than 15 percent today. The number of new drugs entering clinical trials and owned by U.S. firms has steadily dropped in the past 20 years.

Further, the percentage of world pharmaceutical production occurring in the United States has fallen from 50 percent in 1962 to 30 percent in 1968, to 27 percent in 1978. From 1955 to 1962, an average of 46 new drugs were introduced each year in the United States. Today, the average is 17.

I recite these figures to demonstrate that the pace of America's drug innovation is slowing. Our leadership is in jeopardy. Our amendments could help reverse this trend.

Congress not only must provide a better generic approval system, it also must provide meaningful incentives for pioneering pharmaceutical research in this country. We urge you to incorporate our changes into this complex legislation so that a bill can emerge that

truly accomplishes all of its objectives, and that will benefit our mutual constituent, the American consumer.

We stand ready to work with you, the committee, your staff and others in the Senate to enact such legislation.

Thank you, Senator Hawkins. We would be pleased to answer questions.

[The prepared statement of Mr. Willaman follows:]

Tab 39

REGULATION OF NEW DRUG R. & D. BY THE FOOD AND DRUG ADMINISTRATION, 1974

JOINT HEARINGS

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON LABOR AND PUBLIC WELFARE

AND THE

SUBCOMMITTEE ON ADMINISTRATIVE PRACTICE AND PROCEDURE

OF THE

COMMITTEE ON THE JUDICIARY

UNITED STATES SENATE

NINETY-THIRD CONGRESS

SECOND SESSION

ON

EXAMINATION OF NEW DRUG RESEARCH AND DEVELOPMENT BY THE FOOD AND DRUG ADMINISTRATION

SEPTEMBER 25 AND 27, 1974

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FRIDAY, SEPTEMBER 27, 1974

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Articles, publications, etc.—Continued

In this country, bethanidine and debrisoquine have not been approved for marketing. Although propranolol is available, it has not been approved for the treatment of hypertension. Applications for approval of these drugs for hypertension were submitted to our Food and Drug Administration (FDA) many years ago. Debrisoquine was disapproved. Bethanidine and propranolol for hypertension have not been acted on as yet. Reasons given for delay have included, primarily, lack of sufficient evidence of therapeutic benefit. It is possible, however, that if European trials were admitted as evidence propranolol could be approved for such treatment. Until now, foreign trails could not be used to support a new drug application.

The withholding of approval of useful new drugs in the cardiovascular field has been glaringly apparent for at least ten years. Such negativity does not seem to exist in all sections of the FDA. Especially, it is not seen at the administrative level. The fault seems to lie in the individual reviewing officer who is either unable or unwilling to arrive at a fair judgment of the benefit-risk ratio of a new drug. This reluctance results in endless delay and procrastination.

Of course, the public must be protected against toxicity, so far as this is possible. We also must be certain that the effectiveness of a new drug has been adequately demonstrated. Once this information has been obtained, however, a decision to approve or disapprove the new drug should be carried out as expeditiously as possible. If the FDA reviewing officers are unable to do this then they should be circumvented by another mechanism. One suggestion is to utilize review committees of outside consultants. The latter can be selected in such a way as to obviate criticism as to possible conflict of interest. Such review committees could begin by considering cardiovascular drugs that have been under consideration without decision for three years or longer. At a time when the drug treatment of hypertension has assumed great importance, our colleagues from Britain are telling us that we are falling behind. Patients are being deprived of such apparently useful drugs as debrisoquine and bethanidine, and propranolol has not yet received official approval as an antihypertensive agent. If the British physicians have access to these drugs, then American physicians should have them also.

STATEMENT BY J. RICHARD CROUT, M.D., DIRECTOR, BUREAU OF DRUGS, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Mr. Chairman, I am pleased to have the opportunity to appear before your Subcommittee to discuss the "drug lag" from the viewpoint of the Food and Drug Administration (FDA).

Let me begin by stating that there is no question that a "drug lag" exists in the United States in the sense that a significant number of drugs marketed in foreign countries are not available here. In testimony presented to this Subcommittee on August 16, 1974, Commissioner Schmidt indicated that 307 new chemical entities were marketed in the United States between 1960 and 1973. In the same period 590 additional drugs, not available in the United States, were marketed in either England, France, Germany, Italy, or Japan. Thus of all the drugs introduced somewhere in the world during that period, only about one third appeared in the United States. I would like to submit a copy of our August 16, 1974, testimony for the record.

I might add that the United States is not unique in this regard. No country in this survey (which is based on data collected by Paul de Haen, Inc.) had more than 48 percent of the drugs not available in the United States and England has only 32 percent available. Of these 590 drugs marketed overseas, only 196 are of sufficient interest to manufacturers for them to have submitted an IND in the United States, and only 124 of these IND's are currently active. The important issue is therefore not the number of new drugs marketed in this country but whether any are of therapeutic importance, given the many valuable drugs already available in the United States.

In the testimony of August 16, 1974, we presented a listing of every new chemical entity approved in the United States from 1950 through 1973. We furthermore classified each of these drugs as to whether it was an important therapeutic gain (e.g., new treatment for a disease not adequately treated previously), a modest therapeutic gain (e.g., somewhat greater effectiveness or lesser side effects in relation to available therapy at the time) or no therapeutic gain over other drugs available at the time of introduction. An important conclusion

from this analysis is that drugs representing modest or important therapeutic gains have been introduced into the United States at a relatively constant rate since the mid-1950's. There has been a marked decline in the rate of introduction of new chemical entities in general ever since the peak year of 1959, but this decline has been limited, for all practical purposes, to those agents offering little or no therapeutic advantage over already marketed products.

In the August 16 testimony we also indicated that we had gone over every drug listed by Mr. Paul de Haen or Dr. William Wardell as possibly important and marketed overseas, and we promise a status report on all such drugs for which an IND had ever been submitted in the United States. This listing is now available. Our conclusion from study of this list is that there are not therapeutic breakthroughs currently marketed overseas for which an acceptable alternative therapy does not exist in the United States. There are, however, a number of drugs on the list which represent modest therapeutic gains in the sense that they may have somewhat greater effectiveness, fewer side effects, or convenience gains over available alternative therapies in this country.

I would like then to place the "drug lag" in perspective, as we see it. We do not dispute in any way the fact that a large number of pharmaceuticals marketed in countries outside of the United States are not available here. Indeed, we point to that fact as evidence that the high standards for safety and effectiveness mandated by the Congress and the Federal Food, Drug, and Cosmetic Act are being carried out vigorously and honorably. On the other hand, there are selected drugs, which appear to offer modest advantages over currently available therapies, being marketed in many foreign countries earlier than occurs in the United States. In some cases, but fortunately a relatively few, drugs still marketed overseas have been withdrawn from study in the United States for reasons of safety, usually animal toxicity. These examples were cited by Dr. Henry E. Simmons, former Director of the Bureau of Drugs, in his testimony before the Subcommittee on Monopoly of the Select Committee on Small Business on February 5, 1973. In the vast majority of instances, however, the delay of introduction in the United States is related to the time required to conduct controlled clinical trials in support of safety and effectiveness and to conduct the extensive Phase III testing we deem necessary to permit the drug to be released, with full and proper labeling, for general use.

There is, therefore, a societal cost for strong effectiveness and labeling requirements in that drugs are introduced more slowly into this country than certain other countries. It is important that we maintain balance and perspective on this problem so that the overall net effect is beneficial to the health of the American public. We strongly believe that this is the case now. The "drug lag" is, therefore, a real phenomenon and worth continuing attention; but when viewed in perspective, it must be appreciated that it does not involve any drugs which are important therapeutic gains and is an expected consequence of high regulatory standards.

It is relatively easy to understand why the "drug lag" exists. Most new drugs today are developed by large multi-national pharmaceutical firms which can pick and choose the nation in which they wish to do clinical research. The countries of the world vary greatly in their regulatory requirements, and very few in fact have anything comparable to our own IND process which regulates clinical research on new drugs. Drug firms can thus engage in early testing of new drugs far more easily in Germany, France, Italy, and Switzerland, for example, than they can in the United Kingdom, Sweden, Canada, or the United States.

Similarly, they can test marketing opportunities in a variety of countries before making the decision to go through the regulatory process in the United States. In the case of drugs which appear very promising from the start, an IND is usually submitted in the United States before the drug is marketed elsewhere, and, indeed, there are a number of important drugs currently under investigation in the U.S. which may be marketed here ahead of, or simultaneously with, their appearance in other countries. These are the drugs which, by and large, are in the class of important gains.

At this time, I would like to make several points in regard to the "drug lag" issues as it relates to public policy:

1. It is important to recognize that regulatory requirements are an important influence on the availability of new drugs in this country. This is an inevitable result of the exacting standards set by the law for the effectiveness and safety of new drugs. In a complex technological society such as ours, it is essential that we exercise public control over the new drugs proposed as therapeutic agents for the treatment of disease. We believe there is basic societal agreement on this point.

While some may call for repeal of the Kefauver-Harris Amendments of 1962, such calls are in fact not widespread nor very powerful. We do not perceive these Amendments as being fundamentally threatened and hope that the perception of the Congress is likewise.

2. We must also recognize that our goal in the United States is a therapeutic armamentarium which is composed in totality of drugs which are safe and effective. We must have a single standard for all drugs, including those marketed in the years before the effectiveness requirement was adopted. We believe the United States is well ahead of all other countries in the world in meeting this overall goal. The Federal Food, Drug, and Cosmetic Act, as passed by the Congress and administered by the Food and Drug Administration, has been a pioneering venture in drug regulation for the world. The law has required, quite properly, the removal of ineffective drugs as well as the approval of those new drugs which are safe and effective. The United States is the leading nation of the world, not the lagging nation, in achieving a comprehensive approach to *all* drugs and a single high standard for every drug on the market.

3. We must recognize that the laws of this country presume that every new drug is a health gain in the sense that its benefits must exceed its risks. If a drug meets appropriate standards it should be approved, and if it fails to meet these standards it should be disapproved. For some time, the Agency has been under criticism by the medical profession and the drug industry for its alleged failure to approve drugs which are available in other countries. To the extent that this failure of timely approval is due to administrative delays in the FDA, the Agency has reappraised its way of doing things. We believe we have done this honorably in the past several years with resulting important gains in internal procedures and the quality of decisions. But, to the extent that the "drug lag" results from the failure of the industry to provide data of appropriate quality, or the failure of investigators to conduct adequate well-controlled trials, then there is little the FDA can do to correct the situation. The quality of the data in support of safety and effectiveness is now, and always has been, the central issue in determining whether a drug meets appropriate standards.

4. We must also recognize that the deep societal question to which the "drug lag" issue relates is the benefit-risk question. Of basic concern is the degree of risk our society is willing to take in order to have an ever increasing supply of new drug therapies. We point out that the FDA role in this matter is primarily a judicial one. We evaluate carefully the data presented to us, listen to physicians, scientists and consumers, and then make decisions. Those decisions must be made in accordance with legal standards laid down by the Congress. Those who wish to influence our decisionmaking must therefore follow the same ground rules we are required to follow if they wish to be persuasive. Those who want us to act solely on the basis of testimonial evidence thus can never be satisfied with FDA decisions. At the other extreme, those who would essentially exclude all new drugs except important breakthroughs, cannot be satisfied either. While I respect this kind of basic conservatism in medical practice and indeed taught that philosophy during my years in university life, we must recognize that the law as written by Congress is not intended to constrain the supply of new drugs in this country to the minimum essential drugs needed for a parsimonious style of medical practice. It is intended to permit the marketing of all drugs which meet appropriate standards of safety and effectiveness.

In regard to this issue of benefit-risk judgments, I would like to remind the Subcommittee of a point made by Commissioner Schmidt in his testimony before this Subcommittee on September 25, 1974. This testimony said, "By far the greatest pressure that the Bureau of Drugs of the Food and Drug Administration receives with respect to the new drug approval process is that brought to bear through Congressional hearings. In all of our history, we are unable to find one instance where a Congressional hearing investigated the failure of FDA to approve a new drug. The occasion on which hearings have been held to criticize approval of a new drug have been so frequent in the past ten years that we have not even attempted to count them.

"At both the staff level and managerial level, the message conveyed by this situation could not be clearer. Whenever a difficult or controversial issue is resolved by approval, the Agency and the individuals involved will be publicly investigated. Whenever it is resolved by disapproval, no inquiry will be made. The Congressional pressure for negative action is therefore intense, and ever increasing."

Mr. Chairman, in considering the factors which influence benefit-risk decisions in regard to new drugs, I would seek your considered and sensitive appraisal of this double standard in oversight function which has been applied to the Agency ever since the passage of the Kefauver-Harris Amendments. It is essential that every regulatory agency, including the FDA, be held accountable for its decisions, but such accountability must be sought for *all* decisions. Only in this way can the Agency maintain over the long term the balance, strength, and perspective required to administer the law in the even-handed manner as intended by Congress. The health issues involved are too important for us to seek any other course.

Appendixes follow.

APPENDIX A

YEARLY INTRODUCTION OF NEW DRUG PRODUCTS, 1950–73

The data in these lists are derived from FDA files and from the publications of Paul de Haen. FDA believes that the list represents the most accurate data available to date, but there may be a small number of errors remaining, particularly in the 1950's. Like the lists of Paul de Haen, these lists contian drug products that are new salts or esters of previously marketed drugs(N). New dosage forms, etc, are not generally included unless they involves a new salt or ester. In some cases a drug available for many years was first approved in the 1950's, in which case it is listed (e.g. acetaminophen, 1950).

In evaluating the degree of therapeutic gain arising from the availability of a therapuetic gain deemed to have been offered by the drug at the time of its introduction, considering available therapeutic alternatives at the time, without reference to subsequent experience or current status. Thus, certain drugs no longer marketed may be designated as representing important gains. Our criteria were:

A. *Important Therapeutic Gain.*—Drug may provide effective therapy or diagnosis (by virtue of greatly increased efficacy or safety) for a disease not adequately treated or diagnosed by any marketed drug, or provide markedly improved treatment of a disease through improved efficacy or safety (including decreased abuse potential).

B. *Modest Therapeutic Gain.*—Drug has a modest, but real advantage over other available marketed drugs; e.g., somewhat greater effectiveness, decreased adverse reactions, less frequent dosing in situations where frequent dosage is a problem, etc.

These evaluations are tentative, pending further study which is in progress. Ratings given here are, for the most part, by Bureau of Drugs personnel, and are being refined through consultation with authorities in various fields. We are aware that many specific ratings will be controversial, but we believe that the present ratings are useful beginnings, In any case, the ratings are available for criticism and comment and it is possible for any analyst to develop his own lists of important, modest, and no-gain drugs.

1950

Drug name:	*Rating*
Acetaminophen	
Acetoxan	
Alkavervir	A
Amphetamine PO_4 dibasic (N)	
Biphenamine HCl	B
Corticotropin	A
Cortisone acetate	A—
Cyclamate sodium	B
Dicyclomine HCl	
Dimethyl tubocurarine Cl (N)	
Disodium tetrathiodiglycolate	
Ethyl biscoumacetate	
Khellin	
Levararterenol bitartrate	B
Mercumatilin	
Methafurylene Br (N)	
Methafurylene fumarate (N)	
Methantheline Br	
Methdilazine hydrochloride	

Tab 40

INNOVATION AND PATENT LAW REFORM

HEARINGS

BEFORE THE

SUBCOMMITTEE ON COURTS, CIVIL LIBERTIES, AND THE ADMINISTRATION OF JUSTICE

OF THE

COMMITTEE ON THE JUDICIARY HOUSE OF REPRESENTATIVES

NINETY-EIGHTH CONGRESS

SECOND SESSION

ON

H.R. 3285, H.R. 3286, and H.R. 3605

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The Decline in Effective Patent Life of New Drugs

Martin M. Elsman and William M. Wardell

The effective patent life for new chemical entity drugs has fallen sharply in recent years as a result of an increase in the clinical testing period, later starting of clinical testing after the patent application, and quicker issue of patents.

In a recent statement of concern about the state of domestic industrial innovation, the President recommended strengthening the patent system (*1*). That statement implied that the historical role of patent protection as a major stimulus for innovation had weakened. To determine the extent to which the problem affects pharmaceuticals, this paper examines the state of patent protection afforded new drugs.

The Patent Act of 1836 was adopted because of a perceived need to encourage innovation by eliminating the reluctance to disclose an invention. As incentive for disclosure, the Patent Act granted the inventor a 17-year exclusive right to his invention. As the innovative process became uncertain, lengthy, and expensive, patent protection acquired even greater importance.

In the research-based prescription pharmaceutical industry, patents play an important role. Approximately one out of 10,000 compounds initially examined survives the intense scrutiny and demonstrates the potential to justify marketing. The Pharmaceutical Manufacturers' Association surveyed its member companies in 1962, 1967, and 1970 asking for "an estimate of the number of chemicals, compounds, mixtures, filtrates, or other substances obtained, prepared, extracted or isolated for a medical research purpose, and subjected to biological tests or screens." This included material obtained from outside the company. The estimates were 144,559 for 1962, 175,760 for 1967 and 126,060 for 1970, averaging 148,793 items tested per year.

Our studies showed that an average of 15.3 New Chemical Entities (NCEs) were introduced annually from 1962 to 1978. Using these averages, the ratio of chemicals tested per year to NCEs introduced per year is 9725:1.

Bringing that single drug to market has been estimated to cost $54 million in 1976 dollars (*2*). Because of this uncertainty and high cost, patent protection is a necessary incentive for the infusion of capital to stimulate research and development. Since drugs are technically easy to copy, the patent provides the primary protection against imitation and competition.

Another form of protection against competition — one probably not intended by Congress is afforded by the regulatory system of the Food and Drug Administration. The expense involved in seeing a new drug through the demanding system of regulatory review to demonstrate safety and efficacy creates a substantial barrier to entry into the industry.

However, while certain aspects of the regulatory process may offer some protection against competition, other aspects reduce the duration of patent protection that is of commercial value to the original patent holder. Most drug patents are filed when biological activity is first observed (*3,4*). Since this occurs long before the drug receives regulatory approval for marketing, the "effective" patent life will be reduced considerably from its nominal period of 17 years. We will now examine the extent of this reduction, and its change with time.

Time Trend in Effective Patent Life (EPL)

Effective Patent Life (EPL) is defined as the period of patent protection remaining for a drug at the time of U.S. NDA approval (i.e., the time from NDA approval to expiration of the patent). Recent studies (*3,5,6*) show that EPL has declined substantially over the past 15 to 20 years. This trend is generally attributed to the concomitant increase in the time required for human investigation and NDA approval (*3,5*). To examine this hypothesis, we need to analyze the time trends in both EPL and the period from the start of clinical investigation to U.S. NDA approval.

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Methods — The analysis is based on all patented new chemical entities (NCEs) receiving NDA approval from 1966 through 1979 (*a*). The information needed to determine EPL included dates of the start of clinical testing in the U.S., NDA approval, and patent application and issue (*b*).

Data were available for nearly all variables from 1966 through 1979 (*c*).

Sources for the patent data included the patent consultant Louis Leaman, SmithKline Corporation, direct surveys of individual pharmaceutical companies, and various reference sources, including *Chemical Abstracts* and *Official Gazette of the U.S. Patent Office*. For multi-source drugs (i.e., the same drug marketed under different brand names by different companies) only the drug of the original patent holder was included in the averages. Of all 191 NCEs approved from 1966 through 1979, 168 had patents. The data from those 168 drugs were used to calculate EPL.

Of the three types of drug patents (new compound, medical use, and chemical process), a patent on the new compound provides the most reliable protection. To calculate EPL, we used the earliest compound patent listed for a drug. If no compound patent existed, we used the earliest patent, regardless of type.

Data are grouped according to year of NDA approval. For each variable (e.g., time from start of clinical testing to NDA approval), the time difference was calculated for each drug, and those differences averaged for all drugs approved during that year. The averages were plotted and the raw plots smoothed (Figures 1 and 3) according to the "moving median of three" technique of Tukey (*7*).

Drugs tested before 1963: Length of clinical investigation phase — The IND filing dates assigned retrospectively to drugs in clinical trial before August 1962 do not represent the start of clinical testing in the U.S. (*d*).

Thus, the true period of clinical investigation for pre-1963 drugs began earlier than the date represented by retrospective IND filings. Of the 168 patented NCEs approved from 1966 through 1979, 43 had been assigned retrospective IND filing dates. We were able to obtain the date of first U.S. clinical testing in man in the U.S. for 21 of the 43 retrospective filing dates. From this information, we have derived a standard value of 24 months to apply as a correction to the remaining 22 drugs for which this information was unobtainable (*e*).

Effective Patent Life — Figure 1 displays the relationship between the patent and drug development processes, showing the times of NDA approval and the start of clinical testing in relation to the time of patent issue. The data are plotted according to year of NDA approval. EPL, the time from NDA approval to patent expiration, can be read directly from the right-hand ordinate. As shown in the Figure, EPL for pharmaceuticals was

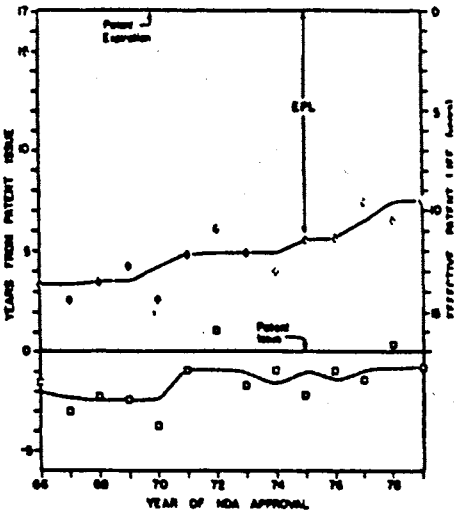

Figure 1.NDA approval (averaged ◇; smoothed ———) and start of clinical testing (averaged □; smoothed — — —), corrected for retrospective IND filings, are plotted in relation to patent issue. Smoothing was done by Tukey's "moving median of three" technique (7).

considerably less than 17 years, even at the beginning of the 14-year study period. It declined from 13.6 years in 1966 to 9.5 years in 1979, a decrease of 4.1 years.

Time from start of U.S. clinical investigation to NDA approval — Figure 1 also shows the pattern (after smoothing (*7*)) of the period from the start of clinical testing to NDA approval during the 14 years from 1966 to 1979. During the 12-year period from 1968 to 1979, EPL dropped by 4.0 years, from 13.5 years to 9.5 years (*f*). The time from the start of U.S. clinical testing to NDA approval increased by 2.4 years (i.e., from 6.9 to 8.3 years) from 1968 to 1979, accounting for 60% of the decrease in EPL (*g*).

Thus the increase in the period from the start of clinical testing to NDA approval accounted for only slightly more than half of the decline in EPL. Therefore, we need to examine the components of EPL in more detail to determine where the remainder of its decline occurred.

Effective Patent Life and the Drug Development Process

From our data (presented later in this paper) we know that the sequence of events in the process of drug development is generally as shown in Figure 2. The sequence begins with the filing of a patent application during the preclinical phase, and continues

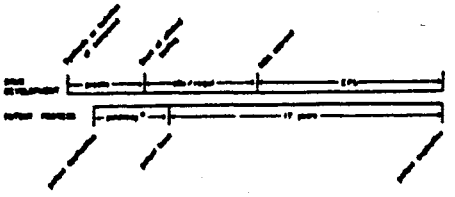

Figure 2/ *Effective Patent Life (EPL) is a function of the timing of the patent application, the pendency period, and the duration of the clinical and regulatory period, as well as the 17-year period of patent protection. *The pendency period is the time from patent application to patent issue.*

with the start of clinical testing, patent issue, NDA approval, and finally patent expiration.

From this pattern and Figure 2, we see that EPL (i.e., the period from NDA approval to patent expiration) is a function of the timing of the patent application, the pendency period, and the duration of the clinical and regulatory periods, as well as the 17-year period of patent protection.

Thus, in addition to its dependence on the duration of the clinical and regulatory periods, EPL depends on two other important factors. It decreases if clinical testing is begun later in relation to the patent application, and conversely will increase if the patent pendency period increases. The final EPL depends on the algebraic sum of the changes in the components.

The changes that occurred in the two additional components of EPL are shown in Figure 3. For the years 1968 and 1979, the two years most representative of the general trend during the study period, the time from patent application to the start of U.S. clinical testing increased 0.5 years (accounting for 13% of the decrease in EPL). The time from earliest patent application to patent issue decreased 1.1 years (accounting for 27% of the decrease in EPL) (h). Coupled with the 2.4 year increase in the period from the start of clinical testing to NDA approval, these changes account for the entire 4.0 year decrease in EPL from 1968-1979. (i)

Discussion/Conclusions

EPL was 13.6 years at the beginning of our study period, 1966. This is considerably less than the 17-year nominal period of patent protection. As time progressed, EPL fell further. This trend is similar to that reported by other investigators (3,5,6). The decrease over time has generally been attributed entirely to an increase in the time between the beginning of clinical testing and NDA approval (3,5), although Statman suggests that this may be responsible for only part of the decrease (6).

Our analysis shows that in the specific sample of NCEs analyzed, almost half of the decline in EPL was caused by two additional factors: An increase in the time between patent filing and clinical testing

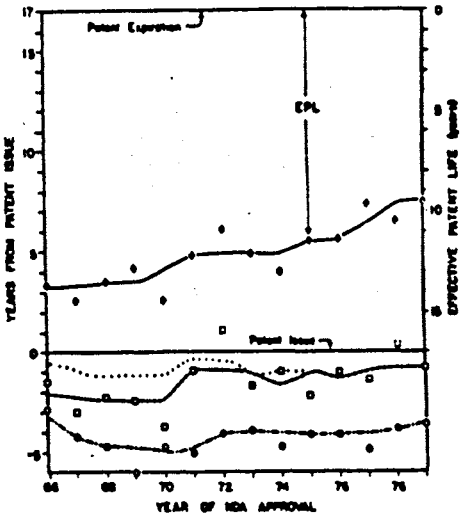

Figure 3/ *Averaged and smoothed values for NDA approval, start of clinical testing, and patent application are plotted in relation to patent issue. The symbols and smoothing are defined as in Figure 1, with the addition of earliest patent filing (averaged ⊙; smoothed —·—) and start of clinical testing, uncorrected for retrospective IND filings (· · · ·).*

and a reduction in the pendency period. It should be noted, as seen in the Figures, that the relative contribution of each of the three components depends to some extent on the years compared.

For the 12-year period from 1968 to 1979, the declining EPL can be explained by two trends. The clinical/regulatory period increased (with all of the increase being in the clinical period), and more of the clinical/regulatory period fell within the period of patent protection (i.e., after the date of patent issue). This latter trend was caused by quicker issue of the patent by the Patent Office (thereby starting the patent clock sooner in the drug development process), and by later starting of the clinical testing.

It should be clearly understood that the "start of clinical testing" being described in this analysis is clinical testing *in the U.S. only*. Although approximately half of the drugs approved in the U.S. originate abroad (10), and a significant fraction of U.S.-originated NCEs are now also first tested clinically abroad (8,9), this study is limited to the U.S. component of the drug development process.

Although a decrease in the pendency period results in earlier issue of patents, it contributes to the erosion of EPL by placing a greater proportion of the clinical/regulatory process within the period of patent protection.

It is not clear why U.S. clinical testing is starting

later in the drug development process realtive to the date of patent application, although one possible reason is the increase in preclinical data requirements prior to first human testing. Related factors, such as compliance with the Good Laboratory Practice (GLP) regulations, could also require more time. Another possibility is that more prolonged initial clinical testing is being done overseas — either by U.S. firms, or because a greater proportion of foriegn-originated drugs are getting U.S. INDs now than previously, either by licensing to U.S. firms, or through foreign-owned sponsoring firms. Further refinement of the data into subsets for self-originated and licensed drugs of U.S. and foreign-owned firms will enable us to examine the latter possibility.

Thus it is clear that the decline in EPL is a result of factors in both the drug development and patent processes. Taking the preclinical and clinical components together, a possible 73% (2.9 years) of the decline in EPL between 1968 and 1979 was accounted for by an increase in components influenced by the IND-NDA regulations, with the remainder of the decline influenced by the Patent Office.

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Footnotes

(a) In this study we define NCEs as compounds of molecular structure not previously marketed in the U.S., excluding new salts or esters, vaccines, antigens, antisera, immunoglobins, surgical products, and diagnostic agents.

(b) For NCEs with INDs filed after 1963, we used the date of IND filing as the start of clinical testing in the U.S. The 30-day waiting period required since August 1970 has a conservative influence on our testing of the hypothesis. As described later, for NCEs that preceded the 1963 IND requirement, we used the actual date of first human administration in the U.S., where available.

(c) All data are complete for NCEs approved from 1966 to 1979, except for the following. Data on start of clinical testing are based on 81% (13 of 16) of patented NCEs for 1977, and 69% (11 of 16) for 1978. Two drugs were excluded from the pendency averages because their pendencies were excessive compared to all other drugs approved during the same years (i.e., 1978 and 1979).

(d) The final IND regulations (Procedural and Interpretive Regulations, New Drugs for Investigational Use) printed in the *Federal Register* of January 8, 1963 required all drug sponsors to submit completed INDs by June 9, 1963 for all drugs in clinical trials as of August 10, 1962. Approximately 1100 drugs were assigned 1963 (i.e., retrospective) IND filing dates during the initial period.

(e) The value of 24 months was obtained by calculating the mean of the available values after eliminating two outlier drugs.

(f) The general trends over the study period are better represented by comparing 1979 with 1968 rather than with 1966. This is shown more clearly in Figure 3.

(g) This period is made up of two components, the IND phase and the NDA phase, which we have examined in detail in other publications (8,9). For the specific set of drugs used in this paper, the mean value of the period from NDA submission to approval was 2.4 years from 1966 to 1972, and 2.2 years from 1973 to 1979. The period of clinical testing increased from a mean of 3.3 years in 1966-1972, to a mean of 4.8 years in 1973-1979.

(h) She used the date of earliest patent filing (including date of foreign claims priority) as an indicator of the company's initial active interest in the NCE.

(i) The dotted line in Figure 3 represents the start of clinical testing, uncorrected for retrospective IND filings. Failing to correct for the retrospective IND filings would substantially underestimate the period of clinical testing and regulatory review (by more than one year from 1966 to 1970). Thus, the uncorrected estimate of the increase in the clinical/regulatory period would be artifactually high by that amount. This could account for the apparent agreement previous authors observed between the decline in EPL and the increase in clinical/regulatory time for the period 1966 to 1976 (5).

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10. W.M. Wardell, M. Hasser and J. DiRaddo, "National origin as a measure of innovative output: The national origin of new chemical entities marketed in the U.S.," Report for the National Science Foundation grant number 78 19066. Also see *Clinical Pharmacology & Therapeutics*, Vol. 19, January 1976, p. 106.

March 18, 1981

MEMORANDUM

TO: Members of the Subcommittee on Courts, Civil Liberties and the Administration of Justice

FROM: Bruce Lehman, Chief Counsel, Subcommittee on Courts, Civil Liberties and the Administration of Justice

SUBJECT: The Patent Term Restoration Issue

You may have been contacted recently by persons seeking your cosponsorship of H.R. 1937, relating to patent term restoration.

You or your staff may find the enclosed article from Research Management Magazine helpful in independently evaluating the issue.

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Research Management, 21 (1): 18-21
1981.

The Decline in Effective Patent Life of New Drugs

Martin M. Eisman and William M. Wardell

The effective patent life for new chemical entity drugs has fallen sharply in recent years as a result of an increase in the clinical testing period, later starting of clinical testing after the patent application, and quicker issue of patents.

In a recent statement of concern about the state of domestic industrial innovation, the President recommended strengthening the patent system (*1*). That statement implied that the historical role of patent protection as a major stimulus for innovation had weakened. To determine the extent to which the problem affects pharmaceuticals, this paper examines the state of patent protection afforded new drugs.

The Patent Act of 1836 was adopted because of a perceived need to encourage innovation by eliminating the reluctance to disclose an invention. As incentive for disclosure, the Patent Act granted the inventor a 17-year exclusive right to his invention. As the innovative process became uncertain, lengthy, and expensive, patent protection acquired even greater importance.

In the research-based prescription pharmaceutical industry, patents play an important role. Approximately one out of 10,000 compounds initially examined survives the intense scrutiny and demonstrates the potential to justify marketing. (The Pharmaceutical Manufacturers' Association surveyed its member companies in 1962, 1967, and 1970 asking for "an estimate of the number of chemicals, compounds, mixtures, filtrates, or other substances obtained, prepared, extracted or isolated for a medical research purpose, and subjected to biological tests or screens." This included material obtained from outside the company. The estimates were 144,559 for 1962, 175,760 for 1967 and 126,060 for 1970, averaging 148,793 items tested per year. (Our studies showed that an average of 15.3 New Chemical Entities (NCEs) were introduced annually from 1962 to 1978. Using these averages, the ratio of chemicals tested per year to NCEs introduced per year is 9725:1.)

Bringing that single drug to market has been estimated to cost $54 million in 1976 dollars (*2*). Because of this uncertainty and high cost, patent protection is a necessary incentive for the infusion of capital to stimulate research and development. Since drugs are technically easy to copy, the patent provides the primary protection against imitation and competition.

Another form of protection against competition — one probably not intended by Congress is afforded by the regulatory system of the Food and Drug Administration. The expense involved in seeing a new drug through the demanding system of regulatory review to demonstrate safety and efficacy creates a substantial barrier to entry into the industry.

However, while certain aspects of the regulatory process may offer some protection against competition, other aspects reduce the duration of patent protection that is of commercial value to the original patent holder. Most drug patents are filed when biological activity is first observed (*3,4*). Since this occurs long before the drug receives regulatory approval for marketing, the "effective" patent life will be reduced considerably from its nominal period of 17 years. We will now examine the extent of this reduction, and its change with time.

Time Trend in Effective Patent Life (EPL)

Effective Patent Life (EPL) is defined as the period of patent protection remaining for a drug at the time of U.S. NDA approval (i.e., the time from NDA approval to expiration of the patent). Recent studies (*3,5,6*) show that EPL has declined substantially over the past 15 to 20 years. This trend is generally attributed to the concomitant increase in the time required for human investigation and NDA approval (*3,5*). To examine this hypothesis, we need to analyze the time trends in both EPL and the period from the start of clinical investigation to U.S. NDA approval.

Dr. Eisman is an Associate in the Department of Pharmacology and Toxicology, University of Rochester School of Medicine and Dentistry. Dr. Wardell is an Associate Professor of Pharmacology, Toxicology and of Medicine, and Director of the Center for the Study of Drug Development, at the University of Rochester School of Medicine and Dentistry. He is also Chairman of the Committee on Government Affairs of the American Society for Clinical Pharmacology and Therapeutics.

Methods — The analysis is based on all patented new chemical entities (NCEs) receiving NDA approval from 1966 through 1979 (*a*). The information needed to determine EPL included dates of the start of clinical testing in the U.S., NDA approval, and patent application and issue (*b*).

Data were available for nearly all variables from 1960 through 1979 (*c*).

Sources for the patent data included the patent consultant Louis Leaman, SmithKline Corporation, direct surveys of individual pharmaceutical companies, and various reference sources, including *Chemical Abstracts* and *Official Gazette of the U.S. Patent Office*. For multi-source drugs (i.e., the same drug marketed under different brand names by different companies) only the drug of the original patent holder was included in the averages. Of all 191 NCEs approved from 1966 through 1979, 168 had patents. The data from those 168 drugs were used to calculate EPL.

Of the three types of drug patents (new compound, medical use, and chemical process), a patent on the new compound provides the most reliable protection. To calculate EPL, we used the earliest compound patent listed for a drug. If no compound patent existed we used the earliest patent, regardless of type.

Data are grouped according to year of NDA approval. For each variable (e.g., time from start of clinical testing to NDA approval), the time difference was calculated for each drug, and those differences averaged for all drugs approved during that year. The averages were plotted and the raw plots smoothed (Figures 1 and 3) according to the "moving median of three" technique of Tukey (*7*).

Drugs tested before 1963: Length of clinical investigation phase — The IND filing dates assigned retrospectively to drugs in clinical trial before August 1962 do not represent the start of clinical testing in the U.S. (*d*).

Thus, the true period of clinical investigation for pre-1963 drugs began earlier than the date represented by retrospective IND filings. Of the 168 patented NCEs approved from 1966 through 1979, 43 had been assigned retrospective IND filing dates. We were able to obtain the date of first U.S. clinical testing in man in the U.S. for 21 of the 43 retrospective filing dates. From this information, we have derived a standard value of 24 months to apply as a correction to the remaining 22 drugs for which this information was unobtainable (*e*).

Effective Patent Life — Figure 1 displays the relationship between the patent and drug development processes, showing the times of NDA approval and the start of clinical testing in relation to the time of patent issue. The data are plotted according to year of NDA approval. EPL, the time from NDA approval to patent expiration, can be read directly from the right-hand ordinate. As shown in the Figure, EPL for pharmaceuticals was

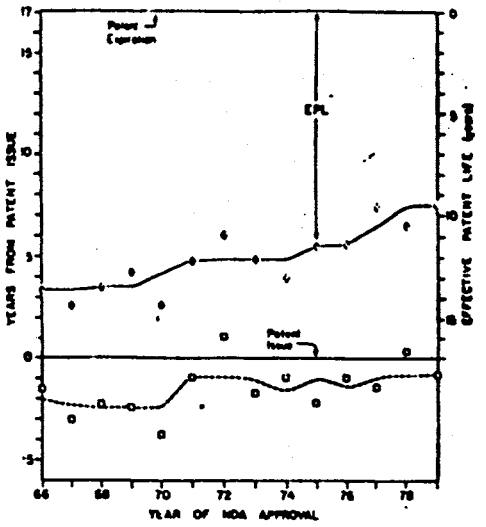

Figure 1 NDA approval (averaged ⊙; smoothed ———) and start of clinical testing (averaged □; smoothed — — —), corrected for retrospective IND filings, are plotted in relation to patent issue. Smoothing was done by Tukey's "moving median of three" technique (7).

considerably less than 17 years, even at the beginning of the 14-year study period. It declined from 13.6 years in 1966 to 9.5 years in 1979, a decrease of 4.1 years.

Time from start of U.S. clinical investigation to NDA approval — Figure 1 also shows the pattern (after smoothing (*7*)) of the period from the start of clinical testing to NDA approval during the 14 years from 1966 to 1979. During the 12-year period from 1968 to 1979, EPL dropped by 4.0 years, from 13.5 years to 9.5 years (*f*). The time from the start of U.S. clinical testing to NDA approval increased by 2.4 years (i.e., from 5.9 to 8.3 years) from 1968 to 1979, accounting for 60% of the decrease in EPL (*g*).

Thus the increase in the period from the start of clinical testing to NDA approval accounted for only slightly more than half of the decline in EPL. Therefore, we need to examine the components of EPL in more detail to determine where the remainder of its decline occurred.

Effective Patent Life and the Drug Development Process

From our data (presented later in this paper) we know that the sequence of events in the process of drug development is generally as shown in Figure 2. The sequence begins with the filing of a patent application during the preclinical phase, and continues

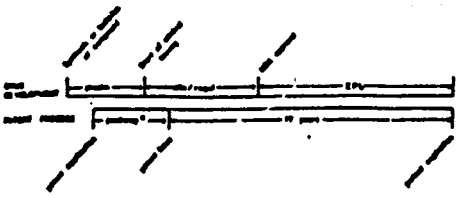

*Figure 2: Effective Patent Life (EPL) is a function of the timing of the patent application, the pendency period, and the duration of the clinical and regulatory period, as well as the 17-year period of patent protection. *The pendency period is the time from patent application to patent issue.*

with the start of clinical testing, patent issue, NDA approval, and finally patent expiration.

From this pattern and Figure 2, we see that EPL (i.e., the period from NDA approval to patent expiration) is a function of the timing of the patent application, the pendency period, and the duration of the clinical and regulatory periods, as well as the 17-year period of patent protection.

Thus, in addition to its dependence on the duration of the clinical and regulatory periods, EPL depends on two other important factors. It decreases if clinical testing is begun later in relation to the patent application, and conversely will increase if the patent pendency period increases. The final EPL depends on the algebraic sum of the changes in the components.

The changes that occurred in the two additional components of EPL are shown in Figure 3. For the years 1968 and 1979, the two years most representative of the general trend during the study period, the time from patent application to the start of U.S. clinical testing increased 0.5 years (accounting for 13% of the decrease in EPL). The time from earliest patent application to patent issue decreased 1.1 years (accounting for 27% of the decrease in EPL) (A). Coupled with the 2.4 year increase in the period from the start of clinical testing to NDA approval, these changes account for the entire 4.0 year decrease in EPL from 1968-1979. (i)

Discussion/Conclusions

EPL was 13.6 years at the beginning of our study period, 1966. This is considerably less than the 17-year nominal period of patent protection. As time progressed, EPL fell further. This trend is similar to that reported by other investigators (*3,5,6*). The decrease over time has generally been attributed entirely to an increase in the time between the beginning of clinical testing and NDA approval (*3,5*), although Statman suggests that it is may be responsible for only part of the decrease (*6*).

Our analysis shows that in the specific sample of NCEs analyzed, almost half of the decline in EPL was caused by two additional factors: An increase in the time between patent filing and clinical testing,

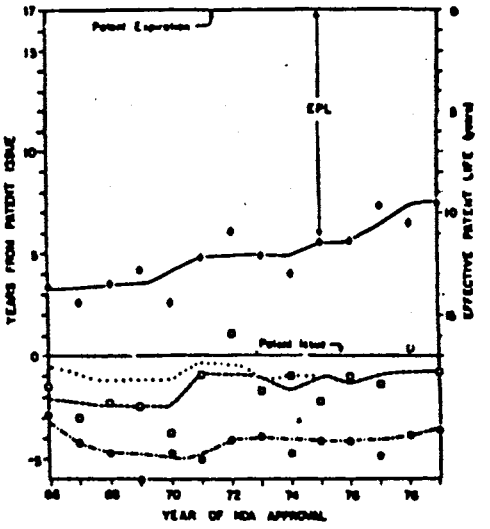

Figure 3: Averaged and smoothed values for NDA approval, start of clinical testing, and patent application are plotted in relation to patent issue. The symbols and smoothing are defined as in Figure 1, with the addition of earliest patent filing (averaged ⊙; smoothed —·—) and start of clinical testing, uncorrected for retrospective IND filings (·····).

and a reduction in the pendency period. It should be noted, as seen in the Figures, that the relative contribution of each of the three components depends to some extent on the years compared.

For the 12-year period from 1968 to 1979, the declining EPL can be explained by two trends. The clinical/regulatory period increased (with all of the increase being in the clinical period), and more of the clinical/regulatory period fell within the period of patent protection (i.e., after the date of patent issue). This latter trend was caused by quicker issue of the patent by the Patent Office (thereby starting the patent clock sooner in the drug development process), and by later starting of the clinical testing.

It should be clearly understood that the "start of clinical testing" being described in this analysis is clinical testing *in the U.S. only*. Although approximately half of the drugs approved in the U.S. originate abroad (*10*), and a significant fraction of U.S.-originated NCEs are now also first tested clinically abroad (*8,9*), this study is limited to the U.S. component of the drug development process.

Although a decrease in the pendency period results in earlier issue of patents, it contributes to the erosion of EPL by placing a greater proportion of the clinical/regulatory process within the period of patent protection.

It is not clear why U.S. clinical testing is starting

later in the drug development process realtive to the date of patent application, although one possible reason is the increase in preclinical data requirements prior to first human testing. Related factors, such as compliance with the Good Laboratory Practice (GLP) regulations, could also require more time. Another possibility is that more prolonged initial clinical testing is being done overseas — either by U.S. firms, or because a greater proportion of foriegn-originated drugs are getting U.S. INDs now than previously, either by licensing to U.S. firms, or through foreign-owned sponsoring firms. Further refinement of the data into subsets for self-originated and licensed drugs of U.S. and foreign-owned firms will enable us to examine the latter possibility.

Thus it is clear that the decline in EPL is a result of factors in both the drug development and patent processes. Taking the preclinical and clinical components together, a possible 73% (2.9 years) of the decline in EPL between 1968 and 1979 was accounted for by an increase in components influenced by the IND-NDA regulations, with the remainder of the decline influenced by the Patent Office.

Acknowledgement

This material is based in part upon work supported by the National Science Foundation under grant #DAR79—17602. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of the National Science Foundation.

Footnotes

(a) In this study we define NCEs as compounds of molecular structure not previously marketed in the U.S., excluding new salts or esters, vaccines, antigens, antisera, immunoglobins, surgical products, and diagnostic agents.

(b) For NCEs with INDs filed after 1963, we used the date of IND filing as the start of clinical testing in the U.S. The 30-day waiting period required since August 1970 has a conservative influence on our testing of the hypothesis. As described later, for NCEs that preceded the 1963 IND requirement, we used the actual date of first human administration in the U.S., where available.

(c) All data are complete for NCEs approved from 1966 to 1979, except for the following. Data on start of clinical testing are based on 81% (13 of 16) of patented NCEs for 1977, and 69% (11 of 16) for 1978. Two drugs were excluded from the pendency averages because their pendencies were excessive compared to all other drugs approved during the same years (i.e., 1978 and 1979).

(d) The final IND regulations (Procedural and Interpretive Regulations, New Drugs for Investigational Use) printed in the *Federal Register* of January 8, 1963 required all drug sponsors to submit completed INDs by June 9, 1963 for all drugs in clinical trials as of August 10, 1962. Approximately 1100 drugs were assigned 1963 (i.e., retrospective) IND filing dates during the initial period.

(e) The value of 24 months was obtained by calculating the mean of the available values after eliminating two outlier drugs.

(f) The general trends over the study period are better represented by comparing 1979 with 1968 rather than with 1966. This is shown more clearly in Figure 3.

(g) This period is made up of two components, the IND phase and the NDA phase, which we have examined in detail in other publications (8,9). For the specific set of drugs used in this paper, the mean value of the period from NDA submission to approval was 2.4 years from 1966 to 1972, and 2.2 years from 1973 to 1979. The period of clinical testing increased from a mean of 3.3 years in 1966-1972, to a mean of 4.8 years in 1973-1979.

(h) We used the date of earliest patent filing (including date of foreign claims priority) as an indicator of the company's initial active interest in the NCE.

(i) The dotted line in Figure 3 represents the start of clinical testing, uncorrected for retrospective IND filings. Failing to correct for the retrospective IND filings would substantially underestimate the period of clinical testing and regulatory review (by more than one year from 1966 to 1970). Thus, the uncorrected estimate of the increase in the clinical/regulatory period would be artifactually high by that amount. This could account for the apparent agreement previous authors observed between the decline in EPL and the increase in clinical/regulatory time for the period 1966 to 1976 (5).

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10. W.M. Wardell, M. Hasser and J. DiRaddo, "National origin as a measure of innovative output: The national origin of new chemical entities marketed in the U.S.," Report for the National Science Foundation grant number 78 19066. Also see *Clinical Pharmacology & Therapeutics*, Vol. 19, January 1976, p. 108.

Tab 41

POLIO IMMUNIZATION PROGRAM, 1976

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON LABOR AND PUBLIC WELFARE UNITED STATES SENATE

NINETY-FOURTH CONGRESS

SECOND SESSION

ON

EXAMINATION ON REASONS FOR THE SHORTAGE OF POLIO VACCINE AND A PROPOSAL FOR ESTABLISHMENT OF A NATIONAL COMMISSION ON VACCINE POLICY

SEPTEMBER 23, 1976

Printed for the use of the Committee on Labor and Public Welfare

U.S. GOVERNMENT PRINTING OFFICE

79-371 O WASHINGTON : 1976

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THURSDAY, SEPTEMBER 23, 1976

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MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY

TO : The Assistant Secretary for Health
Through: ES/PHS _____ _____

DATE: JAN 5 1976

FROM : Director
Center for Disease Control

SUBJECT: Attached Action Memorandum to Secretary, HEW, on Federal Role in Vaccine-Associated Disability - ACTION

In follow-up of discussions with you and your staff concerning the rapidly mounting implications of vaccine-associated disability and at your request, the attached action memorandum for Secretary David Mathews is offered for your review and action.

FACTS

Largely because of court opinions dramatizing the inherent risks of vaccines and vaccine-associated disability, patterns of immunization programming by State and local health agencies and vaccination practices of private medical professionals are being modified. Called-for warnings of inherent risks in vaccines are likely to alarm potential vaccine recipients and result in diminished immunization program effectiveness. Manufacturer liability for vaccine-associated disability, regularly assigned by courts, threatens a predictable vaccine supply--especially of oral polio vaccine--and diminishes the chances of significant independent manufacturer-sponsored research and development of new biologics.

The action memorandum for the Secretary recommends legislation empowering the Department to assume responsibility in managing claims of vaccine-associated disability. This is based on the concept that Federal licensing of biologics, nationally recommended for use in the public interest, imposes a reasonable duty on the government to support persons seriously injured as a result of risks inherent in vaccines recommended and taken for both personal and community protection.

RECOMMENDATION

It is recommended that the memorandum be forwarded to the Secretary for action. The topic is exceedingly timely. Many of the inherent issues on patterns of immunization programming, direct warnings of

TRACER

vaccine recipients by manufacturers, and manufacturer policies on continuing production and distribution of biologics are still in formulation. A decision on the Secretary's part to pursue legislation for public management of vaccine-associated disability would relieve the apprehension and anxiety of public health and medical professionals and of biologics producers.

David J. Sencer, M.D.
Assistant Surgeon General

Tab 42

Calendar No. 856

99TH CONGRESS
2d Session

SENATE

REPORT
99-422

THE PRODUCT LIABILITY REFORM ACT

AUGUST 15 (legislative day, AUGUST 11), 1986.—Ordered to be printed

Mr. DANFORTH, from the Committee on Commerce, Science, and Transportation, submitted the following

REPORT

[To accompany S. 2760]

together with

ADDITIONAL AND MINORITY VIEWS

The Committee on Commerce, Science, and Transportation, having considered an original bill (S. 2760) to regulate interstate commerce by providing for a uniform product liability law, and for other purposes, reports favorably thereon and recommends that the bill do pass.

PURPOSE OF THE BILL

This original bill, S. 2760, as reported, preempts state law to impose major reforms of product liability law in the United States.

The present system in the United States for resolving product liability disputes and compensating those injured by defective products is costly, slow, inequitable, and unpredictable. It does not benefit manufacturers, product sellers, or injured persons. The system's high transaction costs, which exceed the compensation paid to victims, are passed on to consumers; moreover, the unpredictability, uncertainties, and inefficiencies of the system have been linked to the increasing cost and unavailability of liability insurance. Because of the serious burden on interstate commerce created by these product liability problems, federal legislation is needed.

S. 2760, as reported, addresses these problems by making a number of significant reforms that are applicable in all product li-

62-986 O

ability actions in State and Federal courts. These reforms, which include the establishment of an expedited settlement system with incentives for parties to settle claims quickly, will reduce transaction costs and provide greater certainty as to the rights and responsibilities of all those involved in product liability disputes.

Background and Need

INTRODUCTION

Traditionally, product liability has been a matter left to state law, but today the morass of product liability law is a problem of national concern that requires Congressional action. The system of compensating people injured by defective products is costly, slow, inequitable, and unpredictable. It hurts business and consumers as well as our competitive position in world markets.

Many consumers who are injured by defective products and deserve compensation are unable to recover damages or must wait years for recovery. They are caught up with manufacturers and product sellers in a product liability litigation system that has often been characterized as a legal lottery, a system in which identical cases can produce startlingly different results. Moreover, injured victims with the severest injuries tend to receive far less than their actual economic losses, while those with minor injuries are overcompensated.

The inefficiency and unpredictability of the product liability system have been linked to the increasing cost and unavailability of liability insurance. An increasing number of companies, whether they make such products are sporting goods, textile manufacturing equipment, machine tools, medical devices or vaccines, cannot buy adequate insurance coverage. Some have had their insurance cancelled or have experienced reduced coverage with increased deductibles at higher prices. Others cannot obtain coverage at any price.

Thus, the present system has an adverse impact on plaintiffs and defendants, manufacturers, product sellers and consumers. The individual states cannot fully address the problems of the product liability system. Reform at the Federal level is urgently needed.

The Present Product Liability System: Costly, Slow, Inequitable, and Unpredictable

1. Costs

The present product liability system's transaction costs—the costs of litigation, court costs, and attorney's fees—are enormous. Today, plaintiff and defense lawyers collect almost as much from the system as injured victims do; most of the money paid out by manufacturers never reaches the victims at all.[1]

The inefficiency of the present system has been noted often,[2] and has most recently been demonstrated by preliminary study results released July 29, 1986, by the Rand Institute for Civil Justice, which show that the annual overall transaction costs of the U.S. tort system exceed compensation to plaintiffs. The Rand study

[1] Footnotes at end.

found that in 1985, net compensation totaled $13 to $15 billion, but the transaction costs—including plaintiff's attorney's fees, defense legal fees, public expenditures and the time of the litigants—were between $15 billion and $19 billion.[3]

The pattern in product liability cases, alone, is consistent with these findings. According to calculations derived from a comprehensive 1977 survey of 24,452 closed claims conducted by the Insurance Service Office (ISO), for every dollar paid to claimants, insurers paid an average of 42 cents in defense costs.[4] Moreover, for every dollar awarded to a claimant, he or she typically pays a contingent fee of 33 cents in legal costs and therefore receives about 67 cents. Thus, on this basis (adding the average defense cost to the contingent fee) one can estimate that the product liability tort litigation system appears to cost more in litigation and transaction costs than the net recovery received by the claimant.

Not only do these transaction costs exceed compensation, but they have risen dramatically in recent years. According to a 1986 study by economists at New York University, the tort system's administrative or transaction cost—the amount spent to adjust and litigate claims made by injured parties—has been rising rapidly since 1983.[5] This study notes:

> These increases portend trouble ahead if they are not checked. If current rates of growth continue, we can expect that by 1990 we will be spending between $31 and $38 billion per year simply administering the tort system.[6]

With respect to general liability insurance, including product liability, ISO recently reported that the total legal defense expenses incurred in 1984 were $2.7 billion, and that the proportion of general liability costs incurred by insurers that are consumed by legal defense costs has nearly tripled between 1960 and 1984. Most of this growth has occurred recently: the defense costs per dollar paid to claimants doubled in the last decade.[7]

Ordinarily, legal defense costs for product liability claims are paid by insurers; however, because defense costs have escalated so rapidly, the insurance industry has proposed to change the commercial general liability form to include some defense costs within the aggregate limits of the policy. Such a change would only increase the burden of product liability litigation on manufacturers and product sellers, as well as consumers, to whom these costs will ultimately be passed on.

Neither plaintiffs nor defendants benefit from the rapidly increasing and excessive costs of the present system for resolving product liability disputes.

2. Delay

A second problem with the present product liability system is delay. This is particularly a concern for seriously injured victims, who are often in desperate financial straits and must wait years to be compensated while litigation drags on.

One survey has shown that 36 percent of bodily injury losses in product liability cases are not paid until at least 4 years after the first report, and that it takes 5 years to pay the claim with the av-

erage dollar amount of loss. This study also found that "larger claims tend to take much longer to close than smaller ones."[8]

Another, more recent insurance industry study found that the victims of the severest injuries have to wait the longest. This study found that in cases in which payment exceeded $100,000, 21.6 percent of claimants waited more than five years for payment. Only 2.1 percent were paid less than a year after they reported their injury, and 62.6 percent took more than three years to be paid.[9]

The chart below shows the results of this study, which compared earlier data from 1975. (The 1975 figures are in parentheses.)

Claims over $100,000

Number of years between date claim reported to insurer and date claim closed	Number of claimants	Percent of claimants	Percent of total payments
1 year or less	4 (5)	2.1 (4.6)	1.6 (4.3)
Over 1 year to 2 years	21 (17)	11.1 (15.7)	10.9 (15.2)
Over 2 years to 3 years	46 (27)	24.2 (25.0)	23.0 (23.5)
Over 3 years to 4 years	41 (17)	21.6 (15.7)	18.5 (19.1)
Over 4 years to 5 years	37 (27)	19.5 (25.0)	26.8 (20.7)
Over 5 years to 10 years	41 (15)	21.6 (13.9)	19.2 (16.5)

The comparison with the 1975 data shows that the problem of delay has actually worsened. In 1975, 54.6 percent of claimants took more than three years to be paid; five years later that number had risen to 62.7 percent.

Such delays plague even the many product liability cases which are settled before trial. One plaintiff's attorney has explained that even though most cases are settled, "most settlement negotiations get serious only a week or so before trial is scheduled to begin." The pattern has become so dependable that "each week the [lawyer's] firm projects cash flow by estimating the settlement value of the cases set for trial the following week."[10]

Delay also can result in undercompensation of victims. Because many victims of injury—particularly those with the most severe injuries—have inadequate resources to pay for their medical and rehabilitation expenses, they are forced to settle for less than their full losses in order to get some payment because they cannot afford to wait longer without compensation.[11] Studies have shown that when rehabilitation has to be delayed, victims do not recover as fully as they do when the problem is treated promptly.[12]

3. Inequitable compensation

Not only does the present product liability system generate excessive costs and delays; it is unable to compensate fairly injured victims in proportion to their losses. Numerous studies have found that the tort system grossly overpays people with small losses, while underpaying people with the most serious losses.

This disturbing pattern was revealed as early as 1983 by a Columbia University report on auto accidents, and the findings of this report have been independently confirmed in the years since by more than a dozen detailed studies.[13] More recently, the 1977 ISO product liability study found that injured plaintiffs with losses between $1 and $1,000 received, on the average, 859 percent of their

losses, while those with losses of over $1 million received, on the average, 15 percent of their losses (*before* paying their attorney's fees).[14] In general, the study found, compensation exceeded economic loss when losses were below $100,000, and then dropped dramatically below economic loss when the claimant's loss exceeded $100,000.[15]

A 1980 insurance industry study of the largest product liability claims confirmed that the most severely injured victims do not even receive full compensation for their pain and suffering. For every dollar of past and future economic loss, the tort system paid claimants $1.22, but if the standard 33 percent attorney's contingent fee is deducted, these claimants were left with only about 81 cents for every dollar of loss.[16]

Other studies have shown that people with lower incomes and lower educational levels recover far less than their middle class counterparts because they have less access to attorneys, cannot afford to wait as long to recover, and often are not good witnesses.[17]

Reform of the product liability system is essential to assure that those who are injured by defective products are fairly compensated in proportion to their losses.

4. Unpredictability

The excessive costs, delays, and inequities of the product liability system are exacerbated by the inherent uncertainties and unpredictability of the system. Indeed, the present product liability system has been characterized as a latter, in which "[l]awyers' talents, plaintiffs' demeanor, defendants' grit, and the idiosyncrasies of jury composition combine to hand similar victims altogether dissimilar results."[18]

As Professor Jeffrey O'Connell has explained in testimony before the Committee:

> If you are badly injured in our society by a product and you go to the highly skilled lawyer . . . in all honesty [the lawyer] cannot tell you what you will be paid, when you will be paid, or indeed if you will be paid.[19]

The present system's uncertainty is a problem for both manufacturers and consumers injured by defective products. Defendants need greater certainty as to the scope of their liability under the law. Plaintiffs need faster, more certain recovery that fully compensates them for their real losses.

The inherent uncertainty of the system has been linked by commentators to the diversity of legal standards applied in different jurisdictions and the doctrinal mixture of contract and tort law applied in product liability cases.[20] In addition, it has been linked to expanding doctrines of liability,[21] the difficulties in establishing causation and fault, as well as the difficulties in translating nonpecuniary loss (pain and suffering) into pecuniary terms.[22]

The uncertainties and unpredictability of the system affect settlements as well as judgments. Settlement negotiations are sabotaged by the lack of clear standards. With respect to punitive damage claims, for example, uncertainties about liability standards make it difficult for manufacturers to negotiate sensibly.[23]

The burden on American productivity and commerce

The present product liability litigation system has become an enormous burden an American productivity and commerce. It deprives consumers of needed products, limits job opportunities, and weakens our competitive position in world markets.

This burden has been increased by what some have described as a "litigation explosion".[24] The number of product liability cases filed in federal district courts has increased from 1,579 in 1974 to 13,554 in 1985, a 758 percent increase.[25] No corresponding figure is available from state courts, which do not maintain separate statistics on product liability claims, but overall civil caseloads have been rising there as well.[26]

The impact of increasing product liability litigation has been felt by manufacturers for more than a decade, and it has been linked to the present crisis with respect to the unavailability and unaffordability of liability insurance. This crisis has been extensively documented in the press,[27] and the Committee has held several hearings on the problem.[28] At those hearings, witnesses testified that the insurance crisis stems in part from cyclical fluctuations in the insurance industry, but many witnesses also cited as contributing factors growing litigation and claim costs; they linked the insurance problem to the inherent unpredictability of the tort litigation system, as well as the increasing difficulty of predicting potential losses due to expanding concepts of liability.

It has been suggested that the business cycle of the insurance industry and industry practices are entirely to blame for current unaffordability and unavailability problems. This ignores the increase in the overall costs of the tort litigation system—an increase which has been felt as much by self-insurers as well as by those who purchase liability insurance. For example, the City of New York, which is self-insured, has recorded total tort judgments and settlements of more than $100 million for almost every year since 1981, although they never approached that level before. Moreover, the dollar value of New York City's average personal injury settlement rose from $7,127 in 1977 to $31,740 in 1985, an increase of 345 percent.[29]

While insurance prices appear likely to stabilize eventually, analysts have concluded that unless the underlying tort system's costs are reduced, they will do so at a very high level. "Prices will doubtless plateau at some point and at some level, but if current trends continue, it seems clear that this will occur at a height that will institutionalize the price shock that will have occurred in the meantime." [30] Numerous studies of the present insurance crisis have independently reached the same conclusion: the rising cost of the tort system is a fundamental cause of the crisis.[31]

But the insurance crisis is only one element of the burden imposed on American productivity and commerce by the product liability litigation system and the overall tort system. The adverse impact of this burden is felt in many ways, and it is not only a matter of obtaining insurance coverage. Much of the cost of the product liability system is borne today directly by manufacturers and product sellers, because there has been a long, continuing trend toward self-insurance among American businesses. In those

policies that have been sold, deductibles have been increasing while policy limits have been shrinking.

The expense of litigating claims diverts resources from productive efforts. Similarly, excessive management time is diverted from production to assessment of legal claims, and the uncertainties of the system deter the development of new products or product improvements. Clearly, the result is not in the best interest of manufacturers or consumers.

Moreover, faced with the costs and uncertainties of the present system, manufacturers may eliminate a particular product line or terminate operations altogether if the costs of product liability exposure become too burdensome.[32] One survey of the impact of product liability on machinery industries found that 13.5 percent of the companies had dropped product lines, while 11.5 percent had decided not to develop a particular new product.[33] One example illuminates the problem:

> In Virginia, William Perry, an engineer, set up a company to design and build hand and foot controls for cars and vans. Perry's son had been crippled in a motorcycle accident, and the father was appalled when he saw the devices available to handicapped drivers. His company has never been sued, but he recently stopped selling his product nonetheless: his liability insurance premiums went up over 1,000% in one year. Says Perry, "I would have continued this business even at a loss if I could have got a decent premium." [34]

Many other examples have been brought to the attention of the Committee, as well. Puritan-Bennett of Overland Park, Kansas, a leading U.S. manufacturer of hospital equipment, stopped making anesthesia gas machines in 1984 because of rising liability risks. These life-saving machines were once made by half a dozen companies; now the only producers are two foreign-owned firms.[35]

Moreover, concerns about product liability appear to be a major contributor to the dramatic decline in the number of manufacturers of vaccines, which has been accompanied by sharply rising prices. During the 1960's, there were eight manufacturers of the combined vaccine that is used to immunize children against diptheria, whooping cough, and tetanus. Today, only one remains, and the cost of the vaccine has skyrocketed. The price per shot was 45 cents in 1982; no it is $11.40, and most of the increases goes into a fund against lawsuits.[36] In the 1960's there were three manufacturers or oral polio vaccine; now there is one.[37] "If present trends are any indication," one writer has concluded, "it appears that the tort system's vagaries will ultimately drive mass immunization programs out of the private sector altogether.[38]

The general aviation industry is another sector of the economy that has been adversely affected by the product liability system. In 1985, insurance premiums averaged $70,000 per airplane, despite the general aviation industry's best safety record in years. These costs have had a devastating effect on sales—and on jobs. In 1979, more than 17,000 general aviation aircraft were sold by United States Manufacturers. In 1985, such sales has dropped by nearly 90 percent. As a result, tens of thousands of workers have been laid

off, and unemployment in the industry is now over 50 percent. Among only the seven largest manufacturers of general aviation aircraft, employment dropped from 40,000 in 1980 to 13,500 in June, 1986.[39]

The adverse effects of the product liability system have carried over into international trade. American manufacturers and product sellers generally pay product liability insurance rates which are 20 time higher than those in Europe.[40] This disparity is attributable in large part to the uncertainties and costs of the American tort litigation system.[41] As a result of this disparity, American manufacturers and product sellers may be at a competitive disadvantage in both foreign and domestic markets. Insurers generally do not discount premiums where a manufacturer exports it goods, because there is always the possibility that a product-related suit will be brought in the United States. Thus, each U.S. product shipped abroad contains an insurance cost element greater than that of a foreign competitor.[42] With respect to domestic markets, the effect of the current uncertainties in product liability law is similar. The price of imported products can be lower because product liability insurance rates for those products are lower.[43]

The limitations of State efforts at reform

In 1978, the Federal Interagency Task Force on Product Liability, after conducting an 18-month study of the problem, issued a report which suggested that a model product liability act be drafted with the idea that reforms of the system would be enacted at the Federal level.[44] A final version of this model law, known as the Uniform Product Liability Act (UPLA), was published on October 31, 1979.[45]

However, UPLA, which ultimately was offered as a model State law, has not been adopted in full in any State. Over 30 States have adopted some form of product liability statute, and others have enacted more general tort reform measures.[46] The States' efforts have been helpful and are to be encouraged; however, those efforts at State law reform have not resolved the overall problems of the product liability tort litigation system. Most State statutes are not comprehensive and fail to address all the key issues that arise in product liability litigation. Even if an individual State adopted a comprehensive product liability statute so that its own law was clear and predictable, the legal rules would still vary from State to State.

Individual States cannot address the problems of the product liability system effectively, because reform within one State does little to resolve the tort litigation problems facing those who deal in an interstate market. Products are manufactured, sold, used, and insured in a nationwide market. Data show that most products manufactured in a given State are consumed or used outside that State.[47] As a result, manufacturers and product sellers may be involved in product liability actions governed by the law of any State in which they do business. An attempt by any one State to reform the system cannot relieve the overall burden imposed on interstate commerce.[48] In New York State, the Governor's Advisory Commission on Liability Insurance recently reached the same conclusion:

Tab 43

[COMMITTEE PRINT]

THE FOOD AND DRUG ADMINISTRATION'S PROCESS FOR APPROVING NEW DRUGS

REPORT

PREPARED BY THE

SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY

OF THE

COMMITTEE ON SCIENCE AND TECHNOLOGY U.S. HOUSE OF REPRESENTATIVES

NINETY-SIXTH CONGRESS

SECOND SESSION

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LETTER OF TRANSMITTAL AND SUMMARY

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
Washington, D.C., November 25, 1980.

Hon. DON FUQUA,
Chairman, Committee on Science and Technology,
U.S. House of Representatives,
Washington, D.C.

DEAR MR. CHAIRMAN: As you know, on June 19, 21 and July 11, 1979, the Science, Research and Technology Subcommittee of the Science and Technology Committee held a series of oversight hearings on "The FDA's Process for Approving New Drugs." Those hearings were a continuation of an important effort in this area, begun by the Hon. James H. Scheuer, former chairman of the Subcommittee on Domestic and International Scientific Planning Analysis and Cooperation. The speed with which Food and Drug Administration approves new drugs for marketing in the U.S. today has become a frequent target of criticism not only by drug manufacturers seeking to market the drugs but also by physicians wanting to use drugs which they know have been available in other technically advanced countries for months to years. Consumers are also concerned about this process with patients generally wanting the early benefits of new therapeutic advances, but some consumers are more concerned about being protected against possible unforseen side effects of drugs.

I am pleased to submit to you this document based on the Subcommittee's oversight hearings and on the considerable effort of the General Accounting Office.

In general, the Subcommittee hearings confirmed earlier impressions that there is, for certain categories of drugs, a "drug lag" within the United States as compared with some other technically advantaged countries. Examples of major, but not exclusive, factors for delays encountered in the availability of therapeutically important new chemical entities revolve about FDA's drug approval process and include: (1) internal management problems within the FDA, (2) complexity and extensiveness of FDA's guidelines and regulations, and (3) adversarial relationships between FDA and the pharmaceutical industry. The cumulative effect of these and other factors have resulted in well-documented drug availability delays. This has had an impact not only upon the overall wellness of the United States population but also upon the ability and willingness of drug manufacturers to invest in innovative approaches for the treatment of human diseases. A number of recommendations were made by hearing witnesses that would facilitate the FDA drug approval process while still insuring the safety of patients and the public and the efficacy of new prescription drugs introduced into the market place.

As a consequence of these findings, the Subcommittee intends to continue to exercise oversight on the scientific base and its application in FDA, the drug approval process and related guidelines and regulations.

With the cooperation in this endeavor of the FDA, other Congressional Committees, and outside experts, the Subcommittee believes that shortcomings in FDA's drug approval process can be remedied and the availability of therapeutic advances to the public can be maximized.

Sincerely,

GEORGE E. BROWN, JR.,
Chairman, Subcommittee on Science, Research and Technology.

6. DRUGS FOR OTHER DISEASES

A number of other drugs could have made significant improvements in therapeutics if they had been available earlier in the U.S.

Bromocryptine (Parlodel) was approved almost 3 years earlier in Switzerland than its approval in the United States in June 1978. It was approved in the United Kingdom in 1976. Bromocryptine is used to treat an endocrine disorder of the uterus and breast (prolactin inhibition), Parkinson's disease (a nervous system disease common in older people), and acormegaly (an endocrine system disease with a particular affect on the bones). FDA classifies it as an important therapeutic gain for the temporary relief of amenorrhea and galactorrhea.

Cyproterone, was approved 6 years ago in Germany and is used in the treatment of sexual hyperactivity and precocious puberty. It is not approved in the United States.

According to the FDA cyproterone acetate is a potent progestational agent of potential significance being investigated for various indications including benign prostatic hypertrophy, sexual hyperactivity, sexual deviance, and central nervous system effects. IND's were submitted by five sponsors during 1968, 1973, 1974. Clinical trials are currently in progress in phases I and II, with the major research being conducted by individual investigators under research IND's. An alternative progestin available in the United States for the endocrinologic indications only is medroxyprogesterone acetate (Depo-Provera). Cyproterone has been used abroad as an anti-androgen for sexual offenders. Two IND's for this use were submitted by individual research investigators in 1978. A drug useful in the treatment of sexual criminals would be an important therapeutic advance, but major questions of safety and efficacy for this use remain to be clarified according to FDA.

Somatotropin (Asellacrin) is a drug FDA classified as important (A). This drug, which is used to promote growth in children with short stature due to a deficiency of pituitary growth hormone, was approved on July 30, 1976, about 15 months after an NDA was submitted to FDA. Somatotropin was approved for use in Sweden in 1971 and in the United Kingdom and Switzerland in 1972.

Bretylium tosylate is an adrenergic blocker.

Bupivacaine hydrochloride (Marcaine) is a longer-acting local anesthetic agent licensed by Sterling Drug from a Swedish firm. That agent had been marketed in Europe at least since 1967, in the United Kingdom since 1968. After extensive clinical trials sponsored by us in the United States, an NDA was filed with FDA in August, 1970; approval was granted in October, 1972 (26 months later).

Levodopa is an anti-Parkinson agent.

Baclofen (Lioresal), a muscle relaxant was introduced in the United Kingdom in 1972 and approved in the United States in October 1977. It represents a modest therapeutic gain (B) according to FDA.

Danazol (Danocrine) is a gonadotropin. An NDA was filed with the FDA on December 18, 1973 for use in endometriosis, a clinical disorder of women for which no satisfactory medical treatment previously existed. Approval was received on June 21, 1976, a little more

than 30 months later. A submission was made in the United Kingdom on December 27, 1973 and the Republic of Ireland on January 23, 1974. The non-domestic submissions contained only data obtained from studies in the United States, the same data submitted to the FDA. Approval was granted in the United Kingdom on June 6, 1974 (a few days longer than 6 months after submission); approval was granted in Ireland on May 24, 1974 (4 months after submission).

A supplemental application was filed with the FDA on March 6, 1978 for an additional indication, fibrocystic breast disease, already approved in the United Kingdom and Ireland. Action on this submission was still pending at the FDA 16 months later.

Desmopressin (DDAVP), an antidiuretic (B), as introduced in the United Kingdom in 1975 but not approved in the United States until 1978.

Calcitonin is a blood calcium regulator.

Dimethyl sulfoxide (DMSO) can be derived from lignin, the cement substances of trees or can be made from a number of organic chemicals. Although the chemical history of DMSO goes back to 1866, promise of this chemical in the medical sciences was shown in 1959 with the demonstration of its protective effective on red blood cells and other tissues from freezing damage and later with its ability to serve as a "carrier" drug in conveying other substances through the skin and mucous membranes.

In early clinical studies, dimethyl sulfoxide was shown to relieve pain, reduce swelling, slow the growth of bacteria, improve blood supply, soften scar tissue, enhance the effectiveness of other pharmacologic agents, serve as a diuretic, and act as a muscle relaxant.

The first report on the use of dimethyl sulfoxide as a pharmacologic agent was writen in 1963 and published February 1, 1964. The first IND to study DMSO clinically in the United States was submitted on October 25, 1963. Three NDA's on DMSO were submitted to the FDA in 1965. All were turned down. A fourth NDA was submitted in 1970. It was also turned down by the FDA, in spite of mounting evidence in the scientific and medical literature of the potential pharmacological importance of DMSO.

According to Stanley Jacob:

> Of major importance is the fact that DMSO has been shown to be of value, not only in diseases for which there is other known treatment, but in a number of illnesses for which no other effective or low risk treatment is known, such as the painful ulcers of the fingers in patients with scleroderma....
>
> The value of DMSO in other illnesses for which effective pharmacologic treatment does not presently exist, includes severe abacterial prostatitis, Dupuytren's contracture, subcutaneous scarring from cobalt irradiation, keloids, Peyronie's disease and potentially in otherwise "irreversible" injury to the brain and spinal cord....
>
> Dimethyl sulfoxide is a useful adjunct in the treatment of rheumatoid arthritis, degenerative arthritis and gouty arthritis. It primarily will relieve pain, but will also reduce inflammation and increase joint mobility. Due to its effec-

> tiveness in the treatment of arthritis, Americans by the thousands are flocking to nations such as Mexico to receive DMSO. . . .
>
> The effectiveness of DMSO has been demonstrated by comparative studies, by "double blind" studies, and by the clinical impression type of evaluations in man. . . . (and)
>
> A broader spectrum of primary pharmacology and clinical benefit, both actual and potential, has been described in the scientific literature for DMSO than for any other substance with which I am familiar.

In spite of the mounting evidence of the clinical importance of DMSO, it is only prescriptive in the U.S. for interstitial, evstitis (humans) and for acute musculoskeletal problems in large and small animals. DMSO is prescriptive in Canada for scleroderma, in Great Britain and Ireland for shingles when mixed with IDU, and in Germany, Austria and Switzerland for a range of disorders for topical administration. It is also widely prescriptive in South America and has been prescriptive in the U.S.S.R. since 1971. An NDA submitted to the FDA in 1977 on DMSO for scleroderma is currently in an administrative limbo.

In spite of much scientific literature to the contrary, FDA continues to indicate that there is insufficient toxicological information available on DMSO and that the definitive double-masked study on this drug has yet to be done.

Dinoprostone (Prostin E 2), a prostaglandin was introduced in the United Kingdom in 1972. It is used for elective abortion, evacuation of uterine contents in fetal death and the management of benign hydratidiform mole. FDA classifies the drug as a modest therapeutic advance (B) and did not approve it in the United States until August 1977.

Medroxyprogesterone acetate (Depo-Provera), an injectable contraceptive agent, has been approved in many countries around the world. Its NDA for that use has been under consideration by the FDA for over 12 years (since Feb. 1967). Depo-Provera has now been marketed for contraception in over 60 countries and has been used safely for over 6 million woman-years. But on March 7, 1978 FDA ruled it was non approvable in the United States. The reasons why FDA has not approved Depo-Provera have been the subject of another series of congressional hearings conducted by the Select Committee on Population. ("The Depo-Provera Debate", hearings before the Select Committee on Population, U.S. House of Representatives, 95th Congress, second session, August 8, 9, and 10, 1978, U.S. Government Printing Office, Washington: 1978).

Depo-Provera represents an approved indication lag. In 1972, FDA approved this drug for adjunctive therapy and ralliative treatment of certain types of inoperable cancer of the uterus.

Metrizamide (Amipaque) is a breakthrough radiodiagnostic agent licensed by Sterling Drug from a Norwegian firm. An NDA was filed with the FDA on December 27, 1976; approval was granted on August 22, 1978 (20 months later). That agent had been marketed in Scandinavian countries since 1974 and was approved for marketing in the United Kingdom in April 1977 (it is marketed there by the

Norwegian firm). In France, Sterling made a submission on August 22, 1977 and received approval in February 2, 1978 (5½ months later).

Rifampin is an antituberculosis drug.

Trimethoprim is an antibacterial agent.

Vidarabine (VIRA-A) an antiviral, was approved by the FDA in November 1976 but only as an ophthalmic ointment. It is classified as an important therapeutic gain (A) for the treatment of herpes keratoconjunctivitis.

The subcommittee finds that the numerous examples of important or significant drugs which have been delayed and in some cases not yet approved leave no doubt that U.S. patients have suffered a number of significant therapeutic losses. FDA appears to raise safety issues on many drugs which have been in use for years in advanced countries without any problems. These are countries which also are reported to have good post-marketing surveillance programs in operation.

One is lead to the realization that, if the most up to date advances are not available in the United States, there will be a therapeutic deficiency relative to other advanced countries which have these therapies. It follows that some patients denied this benefit will die or suffer unnecessarily. This automatically results in a diminution in the quality of life and the health care of those who are ill.

The United States prescription drug laws were designed to protect citizens by preventing general public access to new drugs which could result in harm to the recipient, if unsupervised. It must be remembered that all drugs have serious potential side effects and all drugs are capable of serious harm if misused or abused. Therefore, safety is relative and both patients and regulators must assume some risk. Levels of public expectations and regulatory goals must be modified to appreciate the necessary balancing of benefits and risks in advancing new and effective drug therapies.

D. The Need for a Variety of Drugs

Although many disease areas have numerous drugs available for their treatment, the subcommittee recognized the need for a variety of drugs for optimum treatment. Drugs not being available simply reduce a physician's and patient's option for the most beneficial treatment for the illness. Discussing sodium valproate, Dr. Farrendelli stated:

> Even with the 15 anticonvulsants available in the United States at this time, only about 50 percent of epilepsy patients could achieve complete control of their seizures. Another 30 percent could achieve partial control and the remaining 20 percent little or no control. More drugs are needed to control seizures in the 50 percent of the epilepsy population for whom presently available therapy doses not provide complete control.

Dr. Zipes summed it up as follows:

> It is as naive to think that one antiarrhythmic drug will be effective for patients, as it is to think that one antibiotic will cure all infections. Therefore, physicians need to be able to choose from a wide selection of antiarrhythmic agents that

have widely different electrophysiologic properties. No ideal universally effective antiarrythmic agent exists. If it did, such questions as to whom to treat and with what drug would not occur. Different causes of an arryhthmia may allow a drug to be effective in one patient but not in another.

Virtually all the available antiarrhythmic agents have significant side effects that may vary from patient to patient. One may produce crippling diarrhea in one patient, and be tolerated without any problems in another. Clinicians must continue to evaluate the benefit-to-risk ratio of any drug and be able to select an effective drug that does not produce side effects for any given patient. To do this, there must be a wide spectrum from which to choose.

Few if any drugs are effective in all patients. In fact, most drugs are effective in only 30 to 75 percent of the patients. Even seemingly unimportant drugs may help a few people and for those few people they are very important.

The subcommittee concludes that the U.S. drug lag has an adverse impact on medical treatment and hence health care in the United States.

Tab 44

VACCINE INJURY COMPENSATION

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT

OF THE

COMMITTEE ON ENERGY AND COMMERCE HOUSE OF REPRESENTATIVES

NINETY-NINTH CONGRESS

SECOND SESSION

ON

H.R. 1780, H.R. 4777, and H.R. 5184

BILLS TO AMEND THE PUBLIC HEALTH SERVICE ACT TO ESTABLISH A NATIONAL VACCINE PROGRAM FOR THE DEVELOPMENT OF NEW VACCINES, THE IMPROVEMENT OF EXISTING VACCINES, COMPENSATION TO THE VICTIMS OF VACCINE-RELATED INJURIES AND DEATHS, TO ENSURE THE SUPPLY OF CHILDHOOD VACCINES, AND FOR OTHER PURPOSES

JULY 25, 1986

Serial No. 99-158

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U.S. GOVERNMENT PRINTING OFFICE

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DTP supply was threatened in 1984 when two major suppliers of DTP threatened to withdraw from the market and production lots did not meet quality control standards. The reports I have seen indicate that current problems related to the supply of vaccines are due to a number of factors including concentration of production in a small number of manufacturers, limited stockpiling of vaccines and commercial companies' participation in the relatively small market for vaccine products.

A third and final factor that threatens the supply of childhood vaccines in our country is the product liability crisis in the area of vaccines. There are a number of factors that need to be carefully evaluated before we make any changes here. First, we need to review how much the current rise in product liability insurance is due to the fluctuating market for insurance. Since 1984, the insurance market has swung from a buyers market to a sellers market. Premium rates have increased by 300 percent and more. Second, we also need to review the impact our Nation's court system, specifically our tort system, has had on the cost and availability of product liability insurance.

I look forward to working with you Mr. Chairman and the other members of the subcommittee in finding the answers to these major issues and moving ahead with the proper legislation to ensure that we continue to have the necessary vaccines at an affordable price.

Mr. WAXMAN. Our first panel of witnesses is comprised of various health organizations that have long been interested in and involved in childhood immunizations and vaccine compensation. Dr. Martin Smith is president of the American Academy of Pediatrics. Malinda Carter is a community health nurse here on behalf of the American Nurses' Association. William Foege is president of the American Public Health Association. Dr. Roy Schwarz is assistant vice president of the American Medical Association. And Dr. Roberta Coffin is commissioner of health for the State of Vermont and is appearing here today as a representative of the Association of State and Territorial Health Officers.

I would like to have you please come forward. We want to welcome each of you to our hearing this morning. Your prepared statements will be made part of the record in full. What we would like to ask each of you to do is to summarize your statement in no more than 5 minutes. I am going to have to be very strict in terms of the 5-minute rule, in order to keep with the schedule that we have planned for today. We will start with Dr. Smith.

STATEMENTS OF MARTIN H. SMITH, PRESIDENT, AMERICAN ACADEMY OF PEDIATRICS; MALINDA CARTER, BOARD OF DIRECTORS, AMERICAN NURSES' ASSOCIATION; WILLIAM H. FOEGE, PRESIDENT, AMERICAN PUBLIC HEALTH ASSOCIATION; M. ROY SCHWARZ, ASSISTANT EXECUTIVE VICE PRESIDENT, AMERICAN MEDICAL ASSOCIATION; AND ROBERTA COFFIN, ON BEHALF OF ASSOCIATION OF STATE AND TERRITORIAL HEALTH OFFICERS

Dr. SMITH. Thank you Mr. Chairman, I am Dr. Martin H. Smith, president of the American Academy of Pediatrics, here today to speak for the academy relative to H.R. 5184, the National Childhood Vaccine Injury Act of 1986.

Mr. Chairman, the academy, first of all, wishes to commend you for providing leadership in this area at a time when leadership is so urgently needed. We also would like to acknowledge the leadership of Mr. Madigan and Mr. Tauke on this issue as well. We applaud your initiative in working with the interested parties to develop H.R. 5184 and putting it forth as a viable means of resolving

the difficult crisis situation that we are facing with respect to our ability to immunize our children against preventable disease.

The crisis has not gone away; it's only shifted from one of supply to one of affordability. While the remaining three producers of our childhood vaccines have stayed in the marketplace, the costs of these products have soared. It is the young parents of our patients who carry this heavy financial burden. For example, the producers of DTP vaccines have tacked an additional $8 charge per shot as a set-aside for their potential liability problems. This means that young parents—and for the most part out of their own pockets—are funding an $80 million liability reserve fund. This is more than we spend as a nation on our entire childhood immunization program.

During the past 2 years particularly, we have had a series of crises of supply and cost and yet somehow the public and the private immunization programs have continued. Both the public and private programs have been strained and this cannot continue.

I have already made reference to the tremendous escalation in costs that has gone on during the past few years and particularly during the past 2 years. In other public statements the academy has called repeated attention to the wide disparity in costs to the private sector of medicine as compared to the costs in the public sector. It is very evident that at the present time the private sector is being forced to bear the largest part of the burden of liability costs. It will inevitably follow that if this disparity continues, many patients will be forced to the public sector for their immunizations when they have been accustomed in the past to receiving them from their own physicians.

The public sector is not capable at the present time of handling this increased load. It has insufficient funding as well as insufficient personnel to manage a large new influx of patients. We recognize the reason for such a wide disparity in costs between the private and public sectors of medicine. The Government is able to purchase vaccines still on their old contracts. When these contracts expire early next year, the Congress must expect that huge increases will also occur in the costs for all vaccines in the public sector.

Mr. Chairman and members of the committee, vaccines are not like other consumer products and must be treated differently from all other products. Their use is mandated by every State in the union and they are already heavily regulated by the Federal Government. The traditional tort system has not served children well in this limited instance and in fact has contributed to this critical public health problem.

The facts are that the number of producers has dwindled, the costs of vaccines have risen dramatically, and research efforts for new and improved vaccines have been chilled. Parents wait for years for the resolution of law suits while the immediate needs of their child are compromised. A few eventually win settlements; many others do not. While we fully recognize the important role the courts play in protecting our children from negligent acts, we commend you for developing legislation which provides for a fair balance between simple and quick compensation and the tort system. You have preserved a parent's right to determine the best

course for their child and you have expedited the process so that the child's needs can be met in an appropriate manner.

We are convinced that there are two steps that can reverse the continually increasing costs of vaccines and the increasing crisis atmosphere surrounding vaccine liability:

First, Congress can push the research and field testing of an improved pertussis vaccine and can see to it that this occurs by incorporating these demands into legislation.

Second, Congress can move forward with a compensation legislation that provides for a prompt and reasonable compensation for all justified claims resulting from vaccine injury.

H.R. 5184 addresses these issues in a fair, compassionate and fiscally responsible manner. We clearly recognize the compromises that must be made. We do have some specific suggestions for modifications in our written statement and look forward to working with the committee on the resolution of these issues.

Mr. WAXMAN. Thank you very much, Dr. Smith. We will look at the suggestions that you have in your prepared statement for some modifications.

Dr. SMITH. All right.

Mr. WAXMAN. We appreciate your testimony.

[Testimony resumes on p. 139.]

[The prepared statement of Dr. Smith follows:]

TESTIMONY

Presented by:

Martin H. Smith, M.D., F.A.A.P.

I am Dr. Martin H. Smith, President of the American Academy of Pediatrics, here today to speak for the American Academy of Pediatrics relative to H.R. 5184, the National Childhood Vaccine Injury Act of 1986.

Mr. Chairman, first of all the Academy wishes to commend you for providing the leadership in this area at a time when leadership is so urgently needed. We applaud your initiative in working with interested parties to develop H.R. 5184 and putting it forth as a viable means of resolving the crisis situation we are facing with respect to our ability to immunize our children against preventable disease.

Mr. Chairman, last summer we witnessed spot shortages of the pertussis vaccine. This experience demonstrates that in the absence of protective legislation our national immunization program is extremely fragile indeed. Let me point out the experience of other countries when pertussis immunization declined:

o The immunization rate in England fell from 79 percent in 1973 to 31 percent in 1978. Beginning in 1977 there was a large outbreak of whooping cough, with an epidemic of 102,500 reported pertussis cases. Between 1977 and 1980 36 pertussis related deaths were reported, as were 5000 hospital admissions due to the disease. These figures may be far too low since pertussis cases and pertussis deaths are underreported and often misdiagnosed.

o In Japan, following two deaths thought to be associated with vaccine administration, the immunization rate declined to between 30 and 40 percent after 1975. In the mid-1970s only 200-400 cases and five or fewer deaths associated with pertussis were reported annually in Japan; in 1980, 13,105 pertussis cases and 41 deaths were reported. 1/

o In Sweden, the highest number of reported cases of pertussis between 1968-1976 was 2,747, and the average was much lower. However, in 1979, the government stopped routine vaccination, and vaccine was not available at all. Pertussis cases since rose to 9,778 cases in 1983. Another peak is expected in 1986-87.

For the moment the crisis has shifted from one of supply to one of affordability. While the remaining three producers of our childhood vaccines have stayed in the marketplace, the costs of these products have soared. The producers of DTP vaccine have tacked on an additional $8 charge per shot as a set-aside for their potential liability problems. This means that young parents are funding an $80 million liability reserve fund (and for the most part are paying for it out of their own pockets). This is more than we spend as a nation on our entire

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1/ Since 1981, the Japanese have been using several different acellular vaccines. It is their practice to start immunization later than in the U. S., sometimes as late as 24 months of age. Limited efficacy data of these vaccines are available.

childhood immunization program! We fear that as a result of price increases many patients will be forced into public clinics for their immunizations. At present, the public sector is not capable of handling this increased load, since it has insufficient funding and personnel to manage a large new influx of patients.

Because of the wide disparity in costs of the vaccine to the private and public sectors of medicine, it is evident that at the present time the private sector is being forced to bear the largest part of the burden of liability costs. This discrepancy in costs between the private and the public sectors of medicine is due to the ability of government to purchase vaccines in bulk under relatively old contracts, which expire early next year. Thus, the Congress must anticipate a huge increases in the costs for all vaccines in the public sector in the near future.

Mr. Chairman, the Academy believes that the crisis atmosphere surrounding childhood vaccines can be reversed only through enactment of legislation containing three key features.

First, the research and field testing of an improved pertussis vaccine must be given the highest priority by government.

Second, a simple, nonadversarial no-fault system providing prompt and reasonable resolution of justified claims resulting from vaccine injury must be established, thus insuring simple justice for children.

Third, the products liability rules applicable to childhood vaccines must be changed in order to provide greater predictability of losses to manufacturers.

Mr. Chairman, legislation supported by the Academy in the past has concentrated on the first two points. We now recognize, based on the crises occurring the past two years, that tort reform also is an essential part of a permanent solution. While we acknowledge the important role the courts play in protecting our children from negligent acts, we commend you for developing legislation which provides for tort reform, as well as a fair compensation system. Vaccines are not like other consumer products and it is appropriate that they be treated differently under products liability law. Immunization is mandated by every state in the Union and childhood vaccines are heavily regulated by the Federal Government. The traditional tort system has not served children well in this limited instance and in fact has contributed to this critical public health problem. The facts are that directly as a result of products liability problems, the number of producers has dwindled, the costs of vaccines have risen dramatically, and research efforts for new and improved vaccines have been chilled. Parents wait for years for the resolution of lawsuits while the immediate needs of their children are compromised. A few eventually win lawsuits and some gain settlements; many others do not.

Mr. Chairman, the Academy believes that H.R. 5184 addresses the three issues outlined briefly above in a fair, compassionate and fiscally responsible manner, and we are supportive of the thrust of this legislation. We do have comments about some specific provisions of the bill and offer suggested revisions for your consideration in the attached Appendix.

Mr. Chairman, we applaud your and Mr. Madigan's efforts--and those of other members of this Subcommittee--directed toward preservation and enhancement of this nation's childhood vaccination program, and the establishment of a fair and just compensation program for injured victims. Thank you for your leadership and your concern for children.

Tab E

Tab 45

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 11, 1989

FROM: Director
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Interpreting Post-marketing Surveillance Information on Halcion.

TO: Members, Psychopharmacologic Drugs Advisory Committee

I. The Halcion Question Delineated:

Halcion, the most commonly prescribed domestic hypnotic drug product, has long been the object of recurring waves of adverse publicity concerning its alleged potential to cause a unique profile of adverse 'behavioral' events. Actually, the adverse behavioral events[1] attributed to Halcion (e.g., excessive sedation, intoxication, bizarre behavior, paradoxical excitement, delirium, psychosis, amnesia, dissociative states, agitation, anxiety, depression, dependence and withdrawal reactions, seizure, even death, etc.) are also reported in association with the use of other benzodiazepine and non-benzodiazepine sedative/hypnotic drugs (e.g., barbiturates, non-BBs). What is unusual about Halcion is the large and sustained volume of reports of already 'labeled' events that continue to be received now some 7 years after its initial introduction into our domestic armamentarium.

Does this volume of reports represent a 'signal' that Halcion is an especially dangerous drug, perhaps one too dangerous to remain on the market as has been implied by some of the drug's more extreme critics? Obviously, after careful review, the agency does not think that it does; to the contrary, despite the volume of reports, we remain convinced that Halcion is a safe and effective hypnotic drug product.

Nevertheless, given the adverse publicity and the anxiety that has been raised among the laity, it seems prudent to have a group of independent experts review the facts about Halcion and discuss

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[1] Importantly, these untoward phenomena are not adverse risks newly discovered through the agency's post-marketing surveillance system. The events enumerated *were recognized as potential or known risks of Halcion prior to its domestic marketing and* were identified, and repeatedly cited, in Halcion's prescription product labeling at the time of its initial marketing.

their possible interpretations, candidly, in an open public forum. Thus, we have come to the Committee.

II. Purposes, Uses and Limitations of the Agency's Post-Marketing Voluntary Reporting System:

Analyses based on data derived from FDA's voluntary spontaneous reporting post-marketing surveillance system will play a prominent role in the Committee's deliberations on Halcion on September 22, 1989. Understanding how our post-marketing adverse event reporting system works and what can and cannot be done with the data it generates is a necessary prerequisite to discussion of these analyses. This memorandum is written to provide some basic insights into the strengths and weaknesses of the system.[2]

To begin, in considering the results of these analyses, Committee members should be mindful that FDA's voluntary spontaneous reporting surveillance system is primarily intended to signal the presence of previously unappreciated drug associated adverse events.[3]

Critically, the voluntary reporting system is not capable of determining the actual incidence of specific adverse events, and consequently, it is not capable of generating reliable estimates of the relative risk of various drug products to cause particular types of adverse events.[4]

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[2] *The accompanying memorandum by Dr. Charles Anello, Deputy Director of the Office of Epidemiology and Biostatistics, which conveys the reporting rate data and discusses our analyses of Halcion, provides additional details about the system. Appendix I of this memorandum also provides additional information.*

[3] *The need for post-marketing surveillance arises because even the most elaborate and extensive of new drug development and testing programs cannot reliably identify drug induced events that occur 1) at low incidence [e.g., less than 1 in 300 to 500 exposures], 2) only or primarily within unique subgroups of the population that were not adequately represented in the drug development clinical testing program, or 3) only or primarily in association with conditions of use not systematically evaluated during pre-marketing clinical testing [e.g., in association with a particular type of concomitant drug therapy or illness].*

[4] *This statement reflects current FDA policy about the legitimate uses of data derived from the agency's post-marketing voluntary spontaneous reporting system. In fact, when releasing information gathered in the system under Freedom of Information, the Division of Epidemiology and Surveillance routinely encloses a 'flier' which warns about potential misuses of data derived from post-marketing spontaneous voluntary reports. (See Appendix I)*

The spontaneous reporting system cannot determine incidence[5] because 1) the number of reports accumulated by the system bear a very uncertain relationship to the number of adverse events actually occurring and 2) the size of the population at risk (i.e., the number of individuals exposed to drug and, therefore, at risk to suffer an adverse drug induced event during the interval for which reports are being accumulated), is unknown.

To elabcrate, counts of reports of adverse drug experience are not counts of drug induced injury. A report of a drug associated event is in almost every case only a speculation that a causal linkage exists between the occurrence of the event and the administration of the drug. Admittedly, in many cases, the speculation is sensible, logical, and reasonably supported by the circumstances in which the event occurred. Nonetheless, the linkage remains a speculation based on a post hoc, ergo propter hoc logic [6]. As Alvan Feinstein long ago pointed out, this form of argument is most persuasive when the event observed is virtually unheard of in the absence of drug treatment (e.g., Feinstein gave the example of the patient who grows feathers on his arm after taking a new drug). However, when the putative drug induced adverse event occurs commonly and spontaneously (i.e., in the absence of drug exposure) in the target patient population, the validity of the post hoc,

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[5] *Incidence is a measure of the rate at which new cases of a particular type (i.e., individuals developing a particular disease or experiencing a specific class of an adverse event) emerge from the population of individuals 'at risk.' Typically, incidence is expressed in terms of new cases per individuals 'at risk' over some convenient interval of time. The calculation of incidence for a particular reporting interval, therefore, requires: 1) a count of all new cases occurring, 2) a count of all individuals in the population who were at risk for becoming cases, and 3) the actual duration of time for which each individual counted at risk was actually at risk. Using this information, an incidence estimate, expressed as cases or events per person-time, can be calculated. Often, however, because information about each individual's actual duration at risk is often unknown, a surrogate incidence estimate, based on the ratio of new cases to all individuals at risk (for any duration of exposure) during the interval of interest is employed.*

[6] *In some cases, a reporter may have additional evidence to support the hypothesis that the observed event is drug induced. Rechallenge of the patient who has recovered from a reversible adverse event is an example of a subject own control, 'n' of one, experiment to assess the question of event causality. For obvious reasons (risk, lack of clinical importance, etc.), rechallenge is not common, however. It is ordinarily reserved for situations where the drug product is unique in its therapeutic potential and especially important to the management of the patient's condition.*

ergo propter hoc argument is itself arguable.

Such a concern is especially relevant to the interpretation of untoward behavioral and/or psychiatric disturbances that are reported after a drug is used in a patient who may be especially prone to exhibit the alleged drug induced behavior in the absence of drug treatment. For example, disturbed sleep is often the initial sign of major psychiatric illness. If the prescriber and patient are not aware of this possibility, the emergence of a full blown psychiatric illness or syndrome may be incorrectly attributed to the hypnotic that was prescribed to treat the initial signs of the illness [7].

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[7] In this regard, it is somewhat ironic that the recent wave of adverse publicity about Halcion arose as the direct result of an alleged Halcion induced illness that might not truly be due to Halcion. Indeed, the particular case serves as a near perfect illustration of the misuse of post hoc ergo propter hoc logic by an uncritical and laregly inadequately informed lay media.

Cindy Ehrlich, the prize winning author of a series of articles highly critical of Halcion that were published in California Magazine in the fall of 1988, unequivocally attributes a several month long episode (characterized by insomnia, agitation, depression, weight loss, suicidal thoughts, and paranoia) that she experienced to taking Halcion. Her opinion as to the cause of her illness was and continues to be given wide credence by the media (20-20, McNeil Lehrer, etc.) although the evidence to support her attribution is circumstantial, primarily tied to the fact that she became progressively more disturbed after Halcion was prescribed for her complaints of insomnia and anxiety. The possibility that her illness had already begun before she took Halcion was never seriously considered by Ms. Ehrlich or the media. In Ms. Ehrlich's view, her insomnia was a result of 'stress' (she was facing a publisher's deadline, she was concerned about her aging mother's housing, her young child's crying was waking her up at night, she had house guests etc.); everything else that subsequently happened was caused by the triazolam her therapist prescribed in response to her initial complaints of insomnia. Ms. Ehrlich's therapist, (who Ms. Ehrlich carefully tells us "..happens to be an M.D."), evidently did not consider Halcion to be the cause of Ms. Ehrlich's worsening clinical state. In fact, she presumably thought the episode was some form of atypical anxiety because she treated Ms. Ehrlich, first with alprazolam and then, when her symptoms worsened, with thioridazine, albeit at a near homeopathic dose of 10mg, soon followed by a low dose (50mg) course of amitryptline. One day, several months into her illness, Ms. Ehrlich, by then taking 4 different psychotherapeutic medicines, abruptly came to the conclusion that her difficulties were caused by Halcion and decided to skip her next dose of Halcion, although she continued to take the other 3 medication (i.e., Xanax, Mellaril and Elavil). By the very next day Ms. Ehrlich claims she felt "if not normal, at least 75% better, even without sleep.' Certainly, Ms. Ehrlich's illness might be a consequence of drug treatment (e.g., some of her complaints are consistent with the signs and symptoms of a treatment emergent benzodiazepine withdrawal reaction), but it is also possible that Ms. Ehrlich's illness was spontaneous, Halcion being but an innocent suspect unfairly indicted and

Thus, the proportion of spontaneously reported adverse events actually caused by drug is invariably unknown. When an event is both common and predicted by the pharmacology of the drug, it may seem quite reasonable to assume that most events of the type reported are caused by the drug, but, even in these circumstances, a substantial fraction of reports received may actually represent spontaneous events.[8]

I raise the issue of attributable risk because a consideration of a drug's proper place in the armamentarium must consider not merely how often its use is associated with some untoward event, but the absolute number of cases actually induced by drug treatment. Herein lies the difficulty. The estimation of attributable risk depends upon a knowledge of incidence which, as has been explained, cannot be determined from spontaneous adverse event reports.

Unfortunately, the inherent limitations of the system are often ignored. It is not uncommon, for example, to see adverse event reporting rates [9] used as surrogates for the incidence of drug

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convicted through careless investigative reporting.

[8] *From an epidemiological perspective, the issue can be thought of as one involving a determination of the 'etiologic fraction' or 'attributable risk.' Etiologic fraction is defined as the proportion of all new cases detected in a given period that are attributable to the risk factor of interest. Unfortunately, it is not possible to estimate the etiologic fraction without knowledge of the incidence of the event in both the absence and the presence of the risk factor (i.e, drug exposure).*

[9] *A reporting rate for a specific drug related ADR is an estimate of the rate at which the agency receives reports of the ADR, the rate being 'adjusted' for the extent of the use of the drug. The adjustment employed relies on an indirect index of drug use derived from the National Prescription Audit (NPA), a scientific sampling of chain and independent pharmacies conducted by a commercial drug information service. Typically, a reporting rate is expressed in terms of reports received per year per million scripts written. The number of scripts written, however, is not a reliable means to estimate the size of the population from which adverse drug events emerge. Because 'scripts written,' only reflects the exposure of ambulatory domestic patients who obtain their drug from scripts filled at pharmacies, it is an inappropriate denominator for calculating reporting rates for events occurring 1) in hospitals or other institutions where a drug can be administered without a prescription being written or 2) in non-domestic settings. It is especially important to consider this fact when making a comparison between the reporting rates of different drug products for the same ADR. Clearly, if one drug is used more commonly in a hospital setting than the one with which it is being compared, the use of agency reporting rates may produce a systematically biased estimate of relative drug*

induced injury. In fairness, if there were a way to do the experiment, we would probably discover that the post-marketing reporting rate for a given ADR-drug dyad 'predicts,' in the sense that statistical regression analysis predicts, the actual incidence of the injury induced by the drug.[10] However, without full knowledge of all the factors affecting reporting rate, there is no reliable means to calculate the absolute incidence of untoward events from information on reporting rates, and, consequently, no way to estimate the etiologic fraction attributable to a specific drug.

Without knowledge of the etiologic fraction, there is really no fair way to compare the risk of two different drugs to cause a given ADR.. Admittedly, in theory at least, using the ratio of the adverse event reporting rates of two products as an indicator of their relative risk to cause a given ADR could be justified if the linkage between adverse event incidence and reporting rate were identical for all products compared. That is, a reporting rate ratio would be proportional to relative risk if the fraction of events detected and the fraction of detected events reported were identical for all products compared. Even then, the reporting rate ratios would not speak to the relative intrinsic risks of the products compared unless the products were being used in the same

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risk. Again, critically, a reporting rate is NOT *an incidence.*

[10]*It is important to acknowledge that there is disagreement about the nature of the probable relationship between incidence and reporting rates. Some drug epidemiologists assert that only a very small fraction of adverse events observed are actually reported. If this is so, the incidence of a drug related event, cited in terms of individuals suffering an event per individuals at risk (i.e., exposed to drug) would be expected to exceed the adverse reporting rate by an order of numerical magnitude or more. For example, the reporting rate for amnesia with Halcion is about 6/10* ^{6} *scripts per year; if we accept the argument that only 10% of observed events are reported, the actual incidence of amnesia would be 60 patients per million exposed per year. This estimate assumes that an average of one script is written per patient. If multiple scripts are written, the true incidence, at least as I have defined it, increases by a factor approximating the average number of scripts written per patient. On the other hand, still other factors tend to make the reporting rate numerically larger than the incidence. First, not every case reported as amnesia actually is one. Second, some proportion of the cases being reported in association with the use of Halcion are probably not caused by Halcion but by other etiologic agents (e.g., illness, concomitant drug use, alcohol, etc.). For additional discussion of this point, see the section of this memorandum describing the findings of my review of a 10% sample of Amnesia reports. [Appendix 2].*

way in the same population at equi-effective doses.[11]

However, because factors[12] influencing reporting rates may NOT be the same for all drug products, it is hazardous to use the ratio of adverse event reporting rates of two drugs as an index of their relative capacity to cause a specific adverse event.

Consequently, a reporting ratio differing from unity must always be treated as a signal of a possible problem, not proof of the existence of one.

This point deserves emphasis because our intra-agency use of comparisons based on the ratio of the reporting rates of Halcion to Restoril may seem implicitly to endorse, <u>despite our official statements to the contrary</u>, the ratio of post-marketing adverse event reporting rates as a valid estimate of relative drug risk.

Not at all! We use reporting rate ratios to explore our large ADR databases for signals of potential problems. We have never advocated that such signals be taken as compelling proof of a differential risk associated with two drug products. This is important to bear in mind because those who obtain FDA documents under FOI are not always so careful. Indeed, even FDA staff sometimes disregard the important distinction between relative risk and relative reporting rates.

In any case, it behooves us to bear in mind that the ratio of reporting rates serves only as a signal of a possible problem, not as proof that one exists!

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[11] The importance of specifying a comparison of risk at equi-effective doses is often neglected. The inequity of comparing the risks of one drug, administered at a relatively subtherapeutic dose, say at an ED_{10}, with one being administered at an ED_{90} should be obvious.

[12] Any number of factors might affect reporting rates although I know of no systematic study of the question. It is generally assumed, however, that reporter motivation can be very important. So, too, logically might be publicity and awareness of the possibility that a drug can cause a particular event. Experts in the UK's CSM (personal communication) have offered this possibility as an explanation for the sudden increase in the frequency of reports linking nomifensine and hemolytic anemia that occurred following CSM warnings about the possible linkage in 1984 and 1985, more than 7 years after nomifensine had been marketed in the UK. Perhaps the most persuasive evidence documenting the existence of such factors is the dramatic fall of adverse reaction reporting on a typical drug in the years following its initial marketing (vide infra).

III. Specific Caveats about the analyses presented which rely on ratios of Halcion to Restoril reporting rates:

Our inter-divisional Task Force[13] recognized from the outset of its efforts that it had no means to extract absolute or relative incidence information from the post-marketing spontaneous reporting data base.[14]

We recognized, however, that even if we could not test the critical implicit assumptions to validate a reporting rate ratio analysis, we ought to carry one out. Based on our knowledge that Restoril was marketed only two years earlier than Halcion, we elected to use it, rather than Dalmane, which had first been marketed in 1970, more than a decade earlier, as the index for our comparison. Dalmane was also considered a bad choice for a comparison agent because of its long acting active metabolite.

In any event, we reasoned that if we found the reporting rate ratios to be unity, the entire issue of Halcion's alleged excess risk would be resolved.

As it turned out, our analysis of the reporting rate ratios found that over all years of their joint marketing, more adverse events were reported for Halcion than for Restoril. Aware that the

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[13] *In the fall of 1988, the surge of publicity surrounding the publication of the Ehrlich articles led the agency to form a special task force, an inter-divisional work group with representatives from the Divisions of Neuropharmacological Drug Products and the Division of Epidemiology and Surveillance, to undertake a systematic review to determine if the charges being made about the alleged excessive risks of Halcion were valid ones. In pursuit of its charge, the task force commissioned a series of analyses, examining, for the first time, annual reporting trends for a series of ADR for both Halcion and Restoril from both direct and manufacturer sources.*

[14] *Other sources can provide such estimates, at least in theory. In fact, UpJohn has conducted a prospective study employing a cohort formed from patients who filled prescriptions in a group of Canadian pharmacies for hypnotics. This study was generally negative, although it did identify an increased risk of amnesia with Halcion. Given our low estimates of the incidence of serious Halcion associated ADRs, however, this is not especially surprising. If Halcion does pose a relatively greater risk than other hypnotics, it is for events that affect only a small proportion of those who use hypnotics. Consequently, the Canadian pharmacy study, because of its small size, and perhaps also because of the fact that 2/3's of the participants were repeat users, was probably incapable by design (i.e, it had inadequate power) of detecting sufficient numbers of these adverse events to gain an estimate of comparative risk.*

interpretation of the analysis depended, in part, upon the assumption that both drugs were being prescribed in the same manner, for the same use, and in the same populations, we attempted to determine if selective prescribing of Halcion by psychiatrists, or its selective use in a uniquely vulnerable population, or the pattern of its actual usage might account for the results. We also examined the possibility that the relative zeal[15] of Halcion's manufacturer for reporting adverse events might account for the differences in observed reporting rates for Halcion and Restoril.

Each of these analyses failed to identify a factor that might explain Halcion's higher reporting rate, but failure to identify the presence of a source of systematic bias in an analysis does not preclude the existence of one. Our analyses of Halcion and Restoril entail comparisons between groups formed without benefit of randomization and must, therefore, be treated with considerable caution.

One good reason for exercising caution is the fact, mentioned earlier, that factors other than absolute ADR incidence exist which strongly affect reporting ratios. Indeed, they are not simply theoretical possibilities but factors with a potency sufficient to cause more than ten fold fluctuations in the reporting rate for the same ADR for a given product over the course of its marketing history.[16]

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[15] *Compared across all products, UpJohn, the sponsor of Halcion, tends to report twice as many adverse events per product as Sandoz, Restoril's sponsor. At one point, agency analysts thought this difference was important and adjusted our Halcion to Restoril reporting rate comparisons accordingly. Our special task force commissioned an analysis of the subset of reports made by physicians directly to the agency to assess the validity of this adjustment. We reasoned that if a sponsor's behavior was affecting reporting rates, an analysis of direct reports would discover different ratios of reporting rates than would one based on manufacturer's reports. As it turned out, our analysis revealed that reporting rate ratios of direct to FDA adverse reporting rates for the two products roughly paralleled the ratios obtained from manufacturer derived reports for all ADRs examined, save deaths.*

[16] *In general, reporting rates tend to be high in the first year or two following the introduction of a drug and then typically decrease over time, reaching some relatively stable asymptotic level of reporting several years after their introduction to the market. Because the pharmacological properties of a drug do not change over time, such changes in reporting rates must be explained by changing patterns of use (e.g., a better understanding within the medical community of how to use the drug or the use of the drug in a less vulnerable population) or a change in event ascertainment and/or reporting.*

Restoril's pattern of reporting is more or less typical. During the first two years following its initial marketing in 1981, its overall ADR reporting rate, given in events per 10^6 scripts, averaged 24.1. From 1984 through 1987, the reporting rate stabilized in the range of 4.1 to 6.7 events per 10^6 scripts, about a 5 fold decrease in reporting rate from the period immediately following its introduction. Somewhat atypically, in 1988, the rate fell even further to 1.5 events per 10^6 scripts, but this may be an artifact of a change in the interval during which reports were accumulated.

In any case, over time, without any known change in its pattern of use, the reporting ratio for adverse events for a hypnotic with a stable sales volume (approximately 5 million scripts have been written annually for Restoril since 1984) has fallen 16 fold! Surely, this historical trend in reporting rate persuasively documents that non-drug related factors strongly affect the number of reports received by the agency.

In contrast, Halcion's historical pattern of reporting is somewhat atypical. Halcion's adverse event reporting rate has dropped only two fold between 1983 and 1988. Importantly, when our Inter-divisional Task Force first examined the annual data in detail (at the end of 1988), the data through the end of 1987 suggested that, like Restoril, Halcion adverse event reporting rates were exhibiting a more typical progressive decrease (i.e., almost four fold over the interval from 1984 through 1987).

Halcion had started off with an average reporting rate of 87.3 events per 10^6 scripts during its first two years of marketing (1983, and 1984), a rate 3.62 times greater than that observed for Restoril during its first two years on the market.[17]
In recent years, however, the gap in reporting rates between Halcion and Restoril has widened; the ratio of reporting rates for was 5.8 in 1987 and 27.3 in 1988. These reporting rate ratios are very unstable, showing wide year to year variation suggesting that they are poor indicators of the relative ability of the two drugs to cause adverse events.

Nonetheless, despite the questionable validity of a reporting rate

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[17] *Comparing these two products at comparable times early in their marketing history may be reasonable because Halcion has continued to suffer adverse publicity throughout its marketing history that Restoril has not. A concern is that adverse publicity might tend to increase event reporting rates. Incidentally, because the number of spontaneous adverse event reports being received by the agency have increased annually throughout this decade, such an approach is still weighted against Halcion which came on the market two years later than Restoril.*

ratio as an indicator of relative risk, the reporting ratio of Halcion to Restoril is consistent with an hypothesis that Halcion is intrinsically a more troublesome drug than Restoril for a small proportion of the population using hypnotics.

IV. The Agency's Halcion Strategy:

Because Halcion appears to be a safe and effective drug for the vast majority of those who use it, and because we had reason to believe that several of Halcion's more important ADRs were dose related, we were not initially disposed to take any immediate publicly visible steps in response to the wave of adverse publicity that occurred in the fall of 1988. In 1987, UpJohn and the agency had agreed that the recommended hypnotic adult and geriatric doses should be lowered [18] and Halcion's labeling had been revised to warn about the possible dose related nature of certain ADRs. A Dear Dr. letter had also been issued to call attention to the changes.

Consequently, when we met with UpJohn in early 1989 to discuss plans for intensifying our surveillance activities and to consider possible additional remedial actions, we were persuaded that it would be premature to take any additional steps until we had had an opportunity to review the effect of the 1987 labeling changes on 1988 adverse reporting rates. In light of these changes and the decreasing trend in reporting rate observed over the 1983 to 1986 interval, both the agency and UpJohn anticipated even further reductions in Halcion's adverse reporting rate for 1988.

As it has turned out, our expectations for a further decline in reporting rate in 1988 were not met. Our 1989 analysis of the 1988 data shows that the reporting rate (41.6 per 10^5 scripts) was nearly double the rates observed in 1987 and 1986 (circa 20 per 10^5 scripts). Of course, this unexpected shift in reporting rate for Halcion may well reflect the effects of a year of especially bad publicity.[19] For example, an increased fraction of events being detected (i.e., a prepared mind phenomena) and/or an increase in the fraction of detected events being reported (i.e., an increased

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[18] *In 1987, 0.25mg, rather than 0.5mg, was made the recommended dose for the typical adult; correspondingly, 0.125mg was recommended for the geriatric patient.*

[19] UpJohn has some evidence to support this hypothesis which they will presumably present to the Committee. A study they commissioned found that in the 4 weeks following a 20-20 broadcast about Halcion, reporting of Halcion associated ADRs was nearly double what it was in the 4 weeks before the broadcast. According to UpJohn, interviews with those reporting these events revealed that the program was often credited with influencing the decision to make the report.

motivation to report) might be the result of increased adverse publicity.

V. What We are asking of the Committee:

First, we would like to learn how the Committee's membership views the signal given by Halcion's reporting rate data. Again, we do not expect the Committee to be able to know precisely what the signal means, but we very much would like its reactions to the information. Risk assessment is always a matter of opinion that depends not only upon expertise and knowledge of 'facts,' but upon one's personal values and beliefs!

Second, we would like to learn what the Committee believes we ought to do from a practical standpoint, if anything, about the reporting rate signal.

As noted earlier, the comments of some of Halcion's more extreme critics imply that Halcion is 'too dangerous' to remain on the market. It seems appropriate to examine this suggestion directly. Can this position be given any credit at all? Obviously, the agency's actions indicate that we do not share this view which we consider extreme and alarmist; as I noted earlier, we believe that Halcion, for most users, is, despite the volume of reports being received, a safe and effective drug. However, some of our critics might argue that the agency's position is self-serving. Thus, it would be useful to learn how you, as independent experts from 'outside' the agency, view the suggestion that Halcion is 'too dangerous' to remain on the market.

Others, however, may hold a very different view, arguing that doing anything will only make matters worse, further distorting the reporting rate of Halcion. Is this a credible argument?.

Certainly, the adverse events and untoward phenomena being reported in apparent excess to its market share are already enumerated in Halcion's labeling; consequently, what is the point of calling further attention to them? Why attempt to manage the effects of adverse publicity with labeling changes?

Of course, there is a broad middle ground between these two extreme positions. In fact, a spectrum of possible remedial actions are conceivable although it is impossible to know what effect they might have. Actions to be considered range from minor rearrangements of labeling to major publicity campaigns.

One older proposal, once made for all benzodiazepines, that has resurfaced is the adoption of a patient package insert that would 'sensitize' the user to the possibility that newly emerging symptoms might be drug related.

Certainly, we might provide the prescriber with additional guidance in those areas where we now believe we understand the genesis of ADRs better than we have in the past. For example, using Halcion on West to East flights where the time available for sleep is shortened might be cautioned against strongly.

The Committee's views on such options, and any of their own design, would be appreciated.

We would also like to learn what the Committee thinks about putting information about reporting rates in the labeling. Should this information be presented? If so, how does one communicate what they are and what they mean to the practitioner and patient who may be unfamiliar with the technical complexities of the ratio?

Finally, of course, we would like to hear your thoughts on the broad question of the nature of the risks that society must tolerate if it is to have potent drugs in its Armamentarium.

VI. Summary

The Committee is being asked to review an issue of considerable potential importance. Unfortunately, decisions must be made in the face of uncertainty about issues of fact that are critical elements in any rational analysis of the problem--specifically, knowledge of the absolute incidence, attributable risk and relative risk of Halcion to cause behavioral ADRs.

Paul Leber, M.D.

doc PDAC922L
cc: NDA 17-892
HFD-100: RTemple
HFD-120: Katz
Laughren
Lee
Mille

Tab 46

PB88-224464

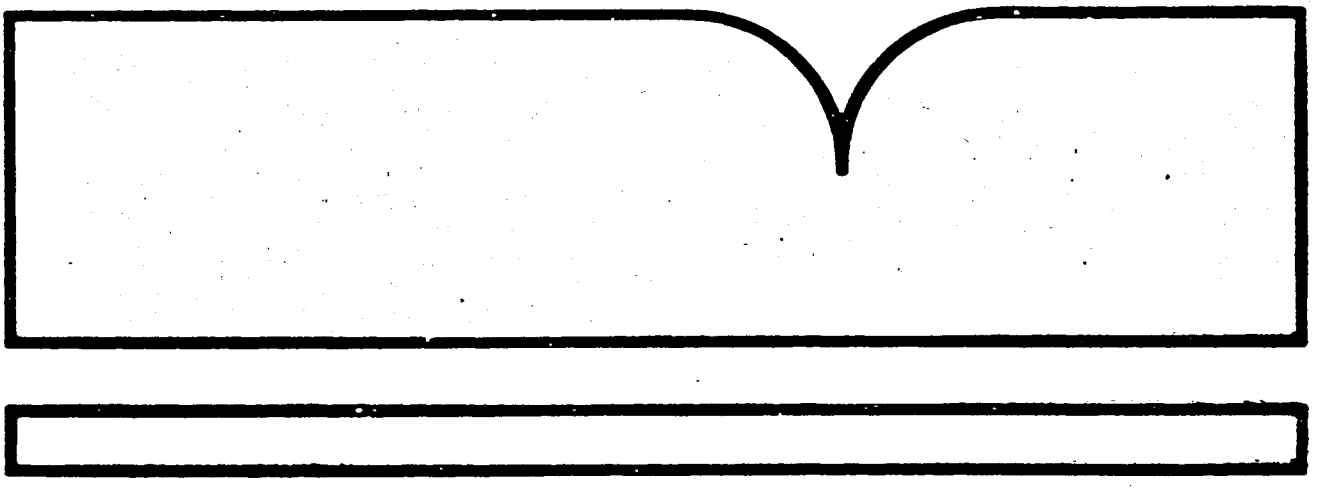
Confronting AIDS (Acquired Immunodeficiency Syndrome) Directions for Public Health Health Care, and Research

(U.S.) Institute of Medicine, Washington, DC

Prepared for

National Research Council, Washington, DC

1986



U.S. Department of Commerce
National Technical Information Service

INSTITUTE OF MEDICINE-NATIONAL ACADEMY OF SCIENCES

Confronting AIDS

Directions for Public Health, Health Care and Research

Confronting AIDS

Directions for Public Health, Health Care, and Research

Institute of Medicine
National Academy of Sciences

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The National Academy of Sciences was established in 1863 by Act of Congress as a private, nonprofit, self-governing membership corporation for the furtherance of science and technology, required to advise the federal government upon request within its fields of competence. Under its corporate charter the Academy established the National Research Council in 1916 and the National Academy of Engineering in 1964.

The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of the appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under both the Academy's 1863 congressional charter responsibility to be an adviser to the federal government and its own initiative in identifying issues of medical care, research, and education.

Support for this project was provided by the National Research Council (NRC) Fund, a pool of private, discretionary, nonfederal funds that is used to support a program of Academy-initiated studies of national issues in which science and technology figure significantly. The NRC Fund consists of contributions from several sources: a consortium of private foundations, including the Carnegie Corporation of New York, the Charles E. Culpeper Foundation, the William and Flora Hewlett Foundation, the John D. and Catherine T. MacArthur Foundation, the Andrew W. Mellon Foundation, the Rockefeller Foundation, and the Alfred P. Sloan Foundation; the Academy Industry Program, which seeks annual contributions from companies that are concerned with the health of U.S. science and technology and with public policy issues with technological content; and the National Academy of Sciences and the National Academy of Engineering endowments.

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Abstract

Human immunodeficiency virus (HIV), the cause of acquired immune deficiency syndrome (AIDS), now infects more than a million people in the United States and millions more in other countries. The cases of AIDS reported thus far are only the beginning of the expected toll, because the damage the virus inflicts on the immune system—and the resulting inability of the victim to fight off infections and cancers—may not be apparent until years after initial infection. The epidemic is growing every day, partly because persons who may not know they are infected are spreading the virus. HIV is spread in only a few ways: transmission by anal or vaginal intercourse, by intravenous (IV) drug use, and from mother to fetus or newborn infant now predominate. Infection occurs mostly in young adults, usually the healthiest segment of the population.

A sizable proportion of those now infected will, in a few years, progress to severe disease and death. If the spread of the virus is not checked, the present epidemic could become a catastrophe. The Institute of Medicine-National Academy of Sciences Committee on a National Strategy for AIDS therefore proposes perhaps the most wide-ranging and intensive efforts ever made against an infectious disease. The situation demands both immediate action to stem the spread of infection and a long-term national commitment to produce a vaccine and therapeutic drugs.

A massive, continuing campaign should begin immediately to increase awareness of ways in which persons can protect themselves against infection, such as using condoms, avoiding anal intercourse, and not sharing drug injection equipment. The campaign should employ all the skills and

tactics of education and media persuasion, and its message should be directed in language understandable to specific target groups, including homosexual men, intravenous drug users, sexually active heterosexuals (especially those who have had a number of partners), and adolescents. The committee estimates that by the end of the decade approximately $1 billion annually, much of it from federal sources, will be needed for education and other public health measures that it recommends, such as blood screening, voluntary confidential testing for infection, and increased efforts in the treatment and prevention of intravenous drug use.

The other arm of the attack on the epidemic is research. The committee believes that a vaccine is not likely to be developed for at least five years and probably longer. One drug has recently shown benefits in the treatment of AIDS, but agents that are acceptably safe for possible long-term treatment and that effectively halt or cure the disease may also not be available for at least five years. The committee calls for extensive basic and applied biomedical investigations to better understand the disease and increase the likelihood of producing a safe and effective drug or vaccine as soon as possible. This program must involve both private industry and the public sector working together. Within the overall research effort there is a need for extensive epidemiologic investigations to assess the spread of infection and the efforts to control it. Finally, there is a need for considerable research on sexual behavior and drug use and factors that influence them.

The committee believes that such a program of research will require at least $1 billion in public funds annually by 1990 and a continuing commitment over many years. These funds must be newly appropriated, not money taken from other research, because the nation's general health efforts as well as those directed against HIV need continuing progress in basic biomedical science on a broad front.

The increasing need for care of patients with AIDS and other HIV-associated conditions, including those with AIDS-related complex and HIV-related dementia, poses new and often difficult problems. These problems will spread widely in the next few years from the populations now affected. The $2- billion yearly expenditure proposed for responding to the epidemic is a small fraction of the billions of dollars for care that the epidemic is sure to cost, especially if it is not rapidly curbed. The optimal organization of care has only begun to be studied in a few cities with the heaviest case loads, but some evidence is emerging to support community-oriented care and minimal hospitalization. The provision of such care should be designed to guarantee equity of access, and the mechanisms for more appropriately financing this care need further evaluation immediately in light of various problems now apparent.

There are scientific and medical lessons to be learned about AIDS and HIV infection elsewhere in the world and compelling reasons for U.S.

involvement in efforts to control the disease worldwide. The committee believes that the United States should be a full participant in international efforts on the problem, both through the World Health Organization and through bilateral efforts.

Federal agencies, notably the Centers for Disease Control, the National Institutes of Health, and the Food and Drug Administration, have contributed enormously to the rapid acquisition of knowledge about AIDS and HIV or to techniques to help in its control. They should continue their efforts, but greater involvement of the academic and private sectors should be encouraged. Continuing evaluation of many matters will be needed, including the spread of HIV, directions for research and development, the effectiveness of various efforts to promote risk-reducing behavior, and the appropriate level of national effort. There is also a need to mobilize existing resources and encourage interaction of the public and private sectors. To fill these needs—and also for informing the American public, Congress, and the executive branch—the committee proposes a National Commission on AIDS, created either as a presidential or joint presidential and congressional entity. The commission should act in an advisory capacity, because the need for integration of the nation's efforts is not presently such as to require central control that supplants the existing administrative structures.

These and other of the committee's major recommendations are summarized at the conclusion of Chapter 1, with detailed recommendations appearing at the ends of major sections within later chapters.

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of the manufacturers) was deleted," and a joint and several liability provision has been modified and now reflects legislation recently enacted in California.

¶ Kimmelman suggested that reform legislation is not needed to enhance international competitiveness of U.S. industry. If product liability laws have forced manufacturing industries overseas, as many proponents of the bill claim, most products would be launched overseas before they are introduced here, the CFA lobbyist argued. However, he maintained that the Roussel-Uclaf oral abortifacient, RU-486, is the only example of a such a product.

¶ CFA has looked for instances of "products that are marketed somewhere else before they are marketed here" and "only found one...and that's a special contraceptive in France," Kimmelman said. CFA "can't seem to find others." Instead, "what we have been seeing is more foreign manufacturers coming in and hiring American workers and manufacturing here under our liability rules," he said.

► Commerce Department Secretary Robert Mosbacher testified that product liability concerns caused Genentech to cancel research into an AIDS vaccine. "The potential liability for that product was so great that [Genentech] abandoned their" research program, Mosbacher said. "That is, in my view, a tragedy for this country." Genentech testified two years ago before the California legislature in support of a state bill to provide product liability protection for AIDS vaccine developers. The firm said the risk of product liability exposure was among the concerns that caused Genentech to drop its AIDS vaccine research project.

¶ Kasten remarked that when Merrell Dow withdrew the anti-emetic ***Bendectin*** from the market, it had annual "sales of $20 mil." but "legal and insurance costs of $18 mil." He added that the decision to withdraw Bendectin was made "despite the petition of 12,000 doctors, who said this product should remain on the market because they need it."

¶ Sen. Rockefeller (D-W.Va.), a cosponsor of the legislation, cited a 1990 Commerce Department "Industrial Outlook" survey of U.S. industry, which found that the current product liability system competitively disadvantages "all" industries that rely on biotechnology. Affected products, he continued, include "pharmaceuticals, vaccines, medical devices, chemicals [and] pesticides."

- 0 -

FDA AND EUROPEAN COMMISSION DISCUSSING GMP MEMORANDUM OF UNDERSTANDING agreement that would apply to all 12 countries that are members of the European Community. Representatives from FDA and the Commission of the European Communities' Directorate General for the Internal Market and Industrial Affairs addressed the development of the good manufacturing practices agreement at the Second Bilateral meeting held March 29-30 at FDA's headquarters in Rockville, Maryland.

¶ A joint statement on the meeting says that the two groups agreed to "the initiation of activities toward the development of a Memorandum of Understanding (MOU) on Good Manufacturing Practices (GMPs)." According to FDA, the agency and the EC contingent concluded that they ought to "start working more diligently" in trying to create such an agreement. One of the commission's highest priorities is to develop an inspection and enforcement system to ensure that all member countries are complying with GMP standards.

The commission told FDA that it would discourage its member countries from negotiating any new MOUs with other countries, but that existing agreements would remain in effect until the EC can develop one as a replacement.

¶ FDA currently does not have any MOUs on GMPs with EC countries; however, the agency has such arrangements with Switzerland, Sweden and Canada. FDA and the EC commission's discussion also applied to MOUs for Good Laboratory Practices (GLPs). FDA has GLP

PRICES OF 5,000 MOST PRESCRIBED DRUGS UP 9.1% IN 1989, Medi-Span reports in its "1989 Inflation Report." The figure is in line with Bureau of Labor Statistics' Producer Price Index figures for the year that put prescription drug inflation at 9.7% ("The Pink Sheet" Jan. 22, p. 14). The PPI, however, is weighted for sales volume, while Medi-Span's data is not.

¶ Of the 5,000 prescription drugs followed by the pharmaceutical tracking firm, Medi-Span reported that 2,595 had price changes during the year. The average price increase for only those items that had price changes is substantially higher, at 14.6%.

Price increases for the top 200 (most prescribed) prescription drug products, however, were only 5.5%. The top 200 products include a total of 568 items (or pack sizes), for which 329 had price changes during the year. The average price hike for the 329 items was 9.5%.

¶ Medi-Span data on 10,000 hospital drug products indicate that prices changed for 4,931 of the products during the year. The average price change for the 10,000 items was 7.2%, while the average increase for the 4,931 products with price changes was 8.1%.

¶ The firm's larger data base on approximately 59,000 prescription, OTC and drug sundries that were marketed throughout the year showed an overall price rise of 5%. Among those products, prices for single-source items rose 5.8%, while prices for multiple-source products rose 4.7%, Medi-Span reported.

- 0 -

SENATE PRODUCT LIABILITY BILL WOULD HAVE SUPPORT OF CONSUMER FEDERATION of America if "three or four" additional changes are made to the legislation, CFA Legislative Director Gene Kimmelman declared at an April 5 hearing before the Senate Commerce/Consumer Subcommittee.

¶ Responding to a comment by the bill's principal sponsor that S 1400 is a moderate and reasonable measure, Kimmelman testified: "I agree with what Sen. Kasten [R-Wis.] said about the changes in his bill. There have been a number of changes made" from the last bill referred to the full Senate by the Commerce Committee. "We think that probably three or four more and we're there," he said. "We're not nearly so far apart as we used to be."

One of the additional changes CFA advocates is deletion of the provision for a defense against punitive damages for firms whose products are approved or rated generally recognized as safe and effective by FDA. The group also opposes the bill's provision to amend the doctrine of joint and several liability.

¶ The Wisconsin Republican commented that the modifications made to his legislation since the 99th Congress have "boxed in" consumer groups, who he suggested must eventually relent in their opposition to the bill. "Increasingly, we are going to have consumers recognize that we don't want to have impediments" to marketing quality products, Kasten said. At some point "the consumer organizations are no longer going to be able to front for the trial lawyers; they're going to have to be off on their own," he declared. At some point "we've got to separate that link, just as we have separated the lawyers [the American Bar Association now supports modified reform legislation] from the [American] Trial Lawyers' Association, which continues to oppose the legislation in any form. "More and more, you're getting boxed in," he said.

¶ Many changes have been made with the approval of consumer advocates, the senator pointed out. For example, he noted, "all limits on damages have now been removed, an expedited claims system has been added...compliance with [industry or government] standards [as a defense against] compensatory damages has been removed...rules that would reduce a worker's right to recover based on employer fault have been deleted, rules eliminating collateral estoppel have been removed, the requirement that plaintiffs prove negligence (a major demand

Tab 48

POSTMARKETING SURVEILLANCE OF PRESCRIPTION DRUGS

NOVEMBER 1982

OTA Reports are the principal documentation of formal assessment projects. These projects are approved in advance by the Technology Assessment Board. At the conclusion of a project, the Board has the opportunity to review the report, but its release does not necessarily imply endorsement of the results by the Board or its individual members.

CONGRESS OF THE UNITED STATES
Office of Technology Assessment
Washington D C 20510

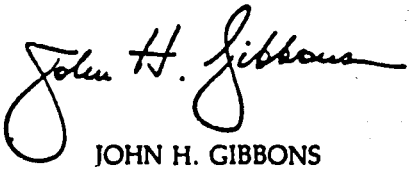
Foreword

Before a drug can be prescribed for use in the United States, it must meet minimum statutory requirements for proof of its efficacy and safety as these have been established by the U.S. Food and Drug Administration (FDA). In premarketing testing, the numbers and types of patients exposed to a drug are necessarily limited compared with the numbers and types of patients who will eventually be prescribed the drug after it is marketed. New uses, contraindications, and side effects of drugs will then inevitably be discovered. Thus, various kinds of postmarketing surveillance have been proposed over the past decade.

A background paper on postmarketing surveillance of prescription drugs was originally being prepared by the Office of Technology Assessment for the project on strategies for medical technology assessment, as requested by the House Committee on Energy and Commerce and its Subcommittee on Health and the Environment. At the further request of that committee and its subcommittee, that background paper was expanded into this full report, *Postmarketing Surveillance of Prescription Drugs.*

Current interest in drug regulation is also focused on the premarketing approval process, because the process has been criticized as unnecessarily delaying the release of valuable drugs in this country. As a result of such criticism, efforts are underway to shorten the approval process through administrative changes within FDA's Office of Drugs, and through revisions of the regulatory interpretations of the statutory requirements for "adequate tests" of a drug's safety and "substantial evidence" of its effectiveness.

This report describes the drug approval process, the history and objectives of postmarketing surveillance, the methods employed to accomplish it, and current activities in postmarketing surveillance. The report provides guidelines to determine whether shortening the drug approval process by various means would diminish its ability to detect adverse drug reactions prior to a drug's release for marketing. The report also identifies oversight issues and options for increased postmarketing surveillance both in the case that Congress decides to relax premarket approval requirements and in the case that it does not.



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Glossary of Acronyms

ADAMHA	Alcohol, Drug Abuse, and Mental Health Administration (PHS)
ANDA	abbreviated new drug application
ADR	adverse drug reaction
CDC	Centers for Disease Control
CDS	Center for Drug Surveillance
CFR	Code of Federal Regulations
DEA	Drug Enforcement Agency
DES	diethylstilbestrol
DHHS	Department of Health and Human Services
DRA	drug regulatory authority
ETIP	Experimental Technology Incentives Program (NBS)
FDA	Food and Drug Administration
HMO	health maintenance organization
IND	investigational new drug
NBS	National Bureau of Standards (Department of Commerce)
NCHS	National Center for Health Statistics (DHHS)
NCI	National Cancer Institute (NIH)
NDA	new drug application
NIDA	National Institute on Drug Abuse (ADAMHA)
NIH	National Institutes of Health (DHHS)
NHLBI	National Heart, Lung, and Blood Institute (NIH)
PHS	Public Health Service (DHHS)
PMS	postmarketing surveillance
SOAR	screening of adverse reactions (method)
U.S.C.	United States Code
WHO	World Health Organization

1.
Summary

1. Summary

INTRODUCTION

To market a drug, the manufacturer must provide evidence of its efficacy and safety to the U.S. Food and Drug Administration (FDA). Once these premarketing requirements are met and the drug has been released, FDA can remove a drug from the market—after giving due notice and an opportunity for a hearing—because of new evidence on the drug's efficacy and safety, the discovery that the drug was approved on the basis of any untrue statement of a material fact, or the failure of the drug to meet manufacturing standards. In cases where a drug may be an "imminent hazard to the public health," FDA can suspend the drug's approval immediately, giving prompt notice of the action and offering the opportunity for an expedited hearing.

In premarketing testing, the numbers and types of patients used to demonstrate a drug's efficacy and safety are limited compared with the numbers and types of patients who will eventually be prescribed the drug after it is marketed. The initial decision to approve a drug for use, however, must be made on the basis of the available knowledge.

Although postmarketing surveillance cannot provide knowledge of the safety or efficacy of drugs at the time of their introduction on the market, various kinds of postmarketing surveillance have been proposed over the past decade to monitor and aid in modifying the use of drugs. The principal focus of postmarketing surveillance proposals has been on the safe use of prescription drugs, even though the range of issues has encompassed both efficacy and safety considerations, e.g., concern over refinements in use as well as better definition of drug risks.

Current interest in prescription drug evaluation and monitoring is focused on the premarketing approval process and the length of time it takes for a drug to be approved by FDA; postmarketing surveillance appears to have waned as a policy issue. Thus, policy formulation and implementation for the premarketing approval process is being pursued without parallel efforts for the postmarketing period.

However, postmarketing surveillance deserves attention as a policy issue for both short- and long-term objectives. Regarding short-term action, if current testing requirements for the premarketing approval process are reduced, pharmaceutical manufacturers could be required to maintain their drug evaluation responsibilities by increasing postmarketing surveillance. Regarding long-term action, postmarketing surveillance remains a policy issue irrespective of current interest in the premarketing approval process: it is only after marketing that a drug's full therapeutic and harmful potentials can be determined.

One way to shorten the premarketing period of the drug approval process would be by reinterpreting the regulations for assessing safety and efficacy. This report provides theoretical and experiential criteria for evaluating how such changes may affect the ability of current guidelines to detect a drug's harmful and beneficial effects. It also discusses the kinds of qualitative changes in the evidence required for drug approval that FDA is implementing. Finally, the report identifies options relating to FDA's postmarketing surveillance. These options could be implemented regardless of whether there is a change in current premarketing drug approval requirements.

THE DRUG APPROVAL PROCESS

A drug's sponsor must provide: 1) "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested;" and 2) "substantial evidence that the drug will have the effect it purports or is represented to have" (21 U.S.C., sec. 355 (d)). This statutory language has led in practice to FDA's establishing a premarketing phase of drug testing that consists of two parts: 1) the investigational new drug (IND) application process, and 2) the filing of a new drug application (NDA).

The IND application describes the investigators' qualifications and the planned clinical trials, the chemical composition of the drug, and data on the pharmacology and toxicology of the new drug collected in animal studies and in prior human studies, if any, such as those conducted in other countries.

The clinical investigations in the IND process are divided into three phases (24):

- *Phase I: Clinical Pharmacology* is that phase in which a drug is first used on humans to confirm dose ranges and pharmacologic effect. The number of subjects in phase I varies depending on the drug, but is usually in the range of 20 to 80 (excluding control patients). Pharmacodynamic and metabolic studies, in whichever stage of investigation they are performed, are considered to be phase I clinical pharmacologic studies.
- *Phase II: Clinical Investigation* consists of controlled clinical trials to demonstrate a drug's effectiveness and relative safety. These are performed on closely monitored patients of limited number, usually 100 to 200 patients, with equal numbers of control patients.
- *Phase III: Clinical Trials* are expanded controlled and uncontrolled trials to gather additional evidence of a drug's effectiveness for specific indications and to more precisely define its adverse effects. Phase III studies observe a total of 500 to 3,000 patients in more natural settings—in clinics, outpatient hospital facilities, and private practice. Phase III usually consists of more than two controlled trials.

After completion of the testing required under the IND application, the sponsor may file an NDA. At least two well-controlled studies establishing each indication for which the drug is intended are required. More than one indication can be established in a single study. (These requirements are under review; see chs. 3 and 6.)

All INDs are classified by chemical type and therapeutic potential, so that those drugs considered by FDA to be of particular therapeutic importance can receive priority review. The highest classification is given to drugs that are new molecular entities (type 1) and that may represent important therapeutic gains (type A)—type 1A drugs.

Several mechanisms are available to FDA to obtain information about drugs once they have been approved for marketing. Once the NDA has been approved, the sponsor is required to monitor information and submit reports about the drug. Other information on adverse drug reactions (ADRs) is monitored by FDA in a number of ways:

- the Spontaneous Reaction Reporting Program, in which information on ADRs is sent to FDA by physicians, pharmacists, and hospitals;
- a monthly review of the medical literature on ADRs (reports and letters to the editors of medical journals, etc.);
- intensive surveillance and epidemiologic studies of ADRs in selected hospitalized and ambulatory populations;
- several specialized registries that collect and analyze possible ADRs;
- in-house monitoring and research studies of such data bases as those of the Medicaid Medical Information Systems of some States and those of commercial sources of drug use data; and
- the World Health Organization, which exchanges reports with FDA, each summarizing the ADRs added to their systems in the previous year.

This postmarketing information is useful for two purposes. First, it may provide the grounds for FDA to remove a drug from the market, when such action is appropriate. Second, it is used by FDA to ensure that limits are placed on advertising and promotional claims and that the drug's labeling is appropriate.

FDA may request further studies when there are questions about a drug that were not sufficiently answered by the phase III studies, but which do not warrant delaying the release of what promises to be a useful new product (24). Although FDA has no explicit authority to require such studies, these "phase IV" studies are almost always performed, as the alternative would be nonapproval of the drug.

HISTORY AND OBJECTIVES OF POSTMARKETING SURVEILLANCE

As a result of 1974 hearings before the Senate Committee on Labor and Human Resources' Subcommittee on Health, the Department of Health, Education, and Welfare formed a Review Panel on New Drug Regulation. The panel issued its report in May 1977 (16).

A bill was subsequently introduced in the Senate in early 1978 to revise the drug provisions of the Food, Drug, and Cosmetic Act. A revised bill, S. 1075, the Drug Regulation Reform Act of 1979, passed the Senate in September 1979. A similar bill, H.R. 4258, was not acted on by the House of Representatives. Included in the Senate bill were the following specifications: 1) drug sponsors could be required to conduct postmarketing surveillance of a drug for up to 5 years; 2) a prescription drug could have its distribution limited if the drug could not otherwise be found to be safe and effective; 3) the standard for a drug's immediate removal from the market would be changed from the drug being an "imminent hazard to the public health" to the less stringent standard of "unreasonable risk of illness or injury to any segment of the population;" and 4) establishment of a "National Center for Drug Science."

During this period, in a speech to the Pharmaceutical Manufacturers Association, Senator Edward Kennedy (D-Mass.) suggested that a better system was needed for monitoring the use and effects of prescription drugs after they were marketed. As a result, the Joint Commission on Prescription Drug Use was established in 1976, funded largely by the drug industry, with the mandate to design a postmarketing surveillance system to detect, quantify, and describe the anticipated and unanticipated effects of marketed drugs, and to recommend a means by which information on the epidemiology of prescription drug use in the United States could be distributed regularly to interested parties. The Joint Commission issued its report in January 1980 (42), but by this time, interest in postmarketing surveillance had waned, and the commission's report and recommendations were little noticed.

In 1976, the year in which the Joint Commission was formed, an interagency agreement was signed between FDA and the Experimental Technology Incentives Program (ETIP) of the National Bureau of Standards in the Department of Commerce. The purpose of ETIP was to provide incentives or reduce barriers to technological innovation through changes in the regulatory process. ETIP's agreement with FDA was to jointly fund a program to determine if improvement in postmarketing surveillance could help reduce the regulatory requirements of the premarketing period, principally those of phase III of the IND process and those of the NDA process. The specific experiment was to develop postmarketing surveillance systems and a method of managing and evaluating the reform (11). The project concentrated on collecting the information required to design these systems (12). By 1982, FDA had assumed most of the funding, as ETIP was to be phased out that year.

A Commission on the Federal Drug Approval Process was convened in mid-1981 to examine how FDA's procedures for the approval of new drugs could be expedited without compromising

public safety and to make recommendations on the development of cost-effective postmarketing surveillance to guarantee the quick withdrawal from the market of drugs that cause significant adverse effects. The commission had its genesis in a joint hearing held in April 1981 by the House Science and Technology Committee's Subcommittee on Natural Resources, Agriculture Research, and Environment and its Subcommittee on Investigations and Oversight. The first meeting was held in July 1981. The commission completed its work and announced its general findings in the spring of 1982, and its printed report was to be released in late 1982.

FDA is examining specific ways to speed up the drug approval process. It is reviewing past phase III trials to see if longer trials or those with large samples have contributed useful information beyond that obtained in phase II and early phase III testing. Past postmarketing studies that FDA required are also being reviewed to see if they provided the information that they were designed to obtain. Data on FDA approval time are being reviewed to see what other factors may slow the approval process. And, as a pilot test, an FDA committee is reviewing the pharmacologic and clinical data on selected drugs at the end of phase II testing, and will make recommendations about the best time for gathering additional information (e.g., phase III v. the postmarketing period) (11).

In March 1982, the FDA Commissioner began a related organization by merging the Bureau of Drugs with the Bureau of Biologics, and replacing the Director of the New Drug Evaluation Division. The merged bureaus have since been designated the National Center for Drugs and Biologics.

Finally, in a related development, the Senate passed by a voice vote, in the first session of the 97th Congress, the Patent Term Restoration Act of 1981 (S. 255). The bill would restore to the term of a patent the time lost in complying with the Government's premarketing testing and review requirements, up to a maximum of 7 years. Patented products eligible for extension would not be limited to human drugs, but would include "human drugs and biologicals, antibiotic drugs, animal drugs and biologicals, food additives, color additives, pesticides, other chemical substances, medical devices, and any other product subject to Federal premarket requirements" (72). In September 1982, the House of Representatives voted on the bill under suspension of its rules. Under such conditions, a two-thirds vote was required for passage, and although the bill received a majority of the votes, it fell just short of the two-thirds majority needed.

METHODS OF SURVEILLANCE

The primary objective of postmarketing studies is to develop information about drug effects under customary conditions of drug use. Initial clues about a drug's potential effects come from the experimental studies carried out with both animals and humans in the premarketing period. Spontaneous or voluntary reporting (e.g., in letters to the editors of medical journals) is the oldest, and to date, the most productive source of new information about a drug's possible effects once a drug is marketed. Other types of studies are used to examine in more detail the possible effects of a drug. In general, these other types of studies use either cohort or case-control methods.

Thus, four types of studies are generally used to identify drug effects: 1) controlled clinical trials, 2) spontaneous or voluntary reporting, 3) cohort studies, and 4) case-control studies (23,50,61,77).

Controlled clinical trials match treatment and control groups as closely as possible, minimize bias through such methods as randomization and "double-blinding," and directly monitor patients for the duration of the study. Controlled clinical trials are considered the most definitive method for evaluating a drug's efficacy and safety, but they are often costly or impractical in specific situations, for example, when a drug's effects are

rare, or appear only after long-term use or a long latency period.

Voluntary reporting by physicians and other health providers, hospitals, and consumers may act to alert FDA and pharmaceutical firms to possible adverse effects of drugs, so that the inference of an association between a drug and an observed health condition may be further studied by cumulative, careful reporting, and confirmed or disconfirmed by more vigorous methods. Underreporting may be a serious deficiency of this method. A drug may also be erroneously associated with an adverse effect until the suspected association fails to show up in repeated, statistically validated studies.

Cohort studies follow a defined group of patients (the cohort) for a period of time. In this method, patients are not randomly assigned to groups, and there is no blinding. Cohort studies are usually prospective and observe the cohort from the beginning of drug use. A group of patients taking the drug of interest is assembled and followed to see, for example, if adverse reactions occur. A second group of patients (the controls) with the same medical condition, who are not taking the drug and who may be receiving alternative treatment, but who are otherwise matched as closely as possible with the cohort, may also be studied in parallel. The control group is used to identify the frequency of occurrence of any condition observed in the drug-exposed group which is due to causes other than the drug (i.e., the "background incidence" of the condition). In this method, patients can be directly monitored to ensure they take the drug appropriately, and to observe the drug's effects; or monitoring can be less controlled. With less control, a larger cohort can be followed, but bias is thus increased.

Case-control studies identify patients with the adverse effects to be studied (the cases), and compare them with a sample (the controls), drawn from the same cohort that gave rise to the cases. Controls are matched as closely as possible with the cases, except with regard to the drug's suspected adverse effect, to examine whether exposure to the drug is the cause. Patients with conditions suspected of being associated with a certain drug would have their medical records reviewed or be interviewed concerning the use of that drug. The histories of the controls would also be studied for information about drug use in the general population. By comparing the proportion of drug users among the cases with the proportion of drug users in the general population, it is possible to infer the relative frequency with which adverse reactions occur in users of certain drugs as compared with nonusers. A sufficient number of appropriate cases must be identified and accurate histories of exposure to drugs must be obtained.

Controlled clinical trials and prospective cohort studies can be used to determine a drug's beneficial as well as adverse effects. Case-control studies are usually used to trace adverse effects back to prior drug use. Voluntary reporting can uncover additional uses of drugs as well as their adverse effects, but reporting of adverse effects is much more common.

The ability of a particular surveillance method to detect a drug's effect depends on two factors: 1) the time that transpires between use of that drug and the occurrence of the drug's effect (the latency period), and 2) how often the effect occurs (its frequency). There are many other determining factors, such as accuracy of observation, and accuracy and completeness of medical records, but these factors present more of a problem in the design of a study's details.

Controlled clinical trials, because of their relatively short duration, will detect only acute or subacute effects. Long-term cohort studies can detect delayed effects, but the data bases necessary for such long-term, large studies are still sparse. Voluntary reporting is usually the way in which long-term effects are first identified. Long-term effects are usually confirmed through retrospective case-control studies, but such studies' reliance on historical data such as medical records can limit their accuracy.

The chance that a particular study will discover a drug effect also depends on the study's sample size and the frequency of the drug effect. For example, in a cohort study, if a drug causes blindness in 1 out of every 100 users (1/100), how many users must be observed to find one case of blind-

ness? If there are 1 million users of the drug, there would be 10,000 users blinded. But in a small sample of only 100 users, the probability of finding one or more cases of blindness would only be 63 percent. If the sample were 200 users, the probability of finding one or more cases would increase to 86 percent. With a sample of 500, the probability would be 99 percent that at least one case of blindness would be found in the observed users.

To state it another way, what number of users would have to be observed to be 95 percent sure of finding one or more cases of blindness when they occur at a frequency of 1 in 100 users? The answer is 300 users, and the general rule is that the number of users in the sample must be three times the reciprocal of the frequency; e.g., for a frequency of 1 in 1,000, the sample would have to be 3,000 to be 95 percent sure of observing at least one case.

Except for some effects that are unique to a specific drug, many drug effects (e.g., stroke, bleeding, skin rashes) are indistinguishable from conditions due to other causes. The "background incidence" of a condition must be known before purported drug effects observed in a study can rightly be attributed to a drug.

Larger sample sizes are needed to determine a drug's effect as the background incidence of a condition increases and as the frequency of a drug's contribution to a condition decreases. For example, given a background incidence of 1/100, as the incidence of a drug's added effect decreases from 1/100 to 1/10,000, the sample size would have to increase from 1,600 to 11 million to remain 95 percent sure of observing at least one case of the added effect. The relationship between background and added incidences is also revealed in considering sample sizes at the extremes. For a known background incidence of 1/1,000 and an added incidence of 1/100, the sample size needed to observe at least one case of the added effect is only 500. But when the background incidence is 1/10 and the added incidence is only 1/10,000, the sample size must be 98 million. These illustrations merely indicate what sample size is required to observe an effect when background incidence is known.

Controlled clinical trials are used primarily for evaluating drug efficacy, not safety, because they are carried out on hundreds, or, at the most, a few thousand drug users. Their use for evaluating drugs already on the market is also limited by their high cost and logistical problems. In fact, the use of controlled clinical trials for determining efficacy alone is already constrained by these two factors (9,46).

These limitations of controlled clinical trials in evaluating the safety of marketed drugs have led to relying on cohort and case-control methods for postmarketing studies. While these latter methods can only indicate an association between a drug and observed conditions, not that the relation is causal (49,77), the cumulative experience of multiple cohort and case-control studies showing consistent associations between a drug and such an effect can lead to a high degree of confidence that the relationship is causal. The most prominent examples of drug studies showing consistent associations are those on oral contraceptives and the risks of cardiovascular disease; similar examples of nondrug studies are those on the risks of smoking.

ISSUES AND OPTIONS

Issue 1:

Revising premarketing tests and shortening the drug approval process.

The efficacy and safety tests in animals and humans specified in FDA regulations for premarketing approval are based on broad statutory language. Efforts to shorten the drug approval process have focused not on the statutory language but on the regulations issued by FDA to implement the law. Thus, the focus here is on oversight issues, not on legislative changes.

Proposals to curtail or eliminate phase III premarketing tests, or shift them to the postmarketing period, can be evaluated both theoretically and experientially.

Theoretically, phase III testing is significantly more sensitive than phase II testing. Adverse effects with an incidence of 1/100 or more are more likely than not to be detected in the 100 to 200 patients given a drug in phase II. But the theoretical sensitivity of detection rises in phase III to 1/500 with 500 patients and to 1/1,000 with 1,000 to 3,000 patients (see ch. 4, table 5).

These observations are relevant to the detection of adverse reactions, but they are not so relevant to the detection of therapeutic effects. Since a drug that helps only 1 in 100 patients would not be very effective, efficacy should be established in phase II. Phase III is intended to gather additional evidence on a drug's effectiveness for specific indications.

If phase III testing were curtailed or eliminated, there is also the question of whether premarketing evaluations would test sufficient numbers of patients to reasonably ensure a drug's safety or give substantial evidence of its efficacy. Even under current regulations, the use of a drug on human subjects is very limited before the drug is released for market: 20 to 80 patients in phase I; 100 to 200 patients in phase II; and 500 to 3,000 patients in phase III—a range of only 620 to 3,280 patients per drug (excluding controls).

In addition to theoretical criteria, experiential criteria could be applied in considering proposals to curtail or eliminate phase III tests. The diminished power to observe adverse drug effects that such changes theoretically entail may not in fact be found, judging on the basis of actual experience in phase III testing, or if it is, it may only concern infrequent, minor effects. Agreement of the experiential data with the differences theoretically expected would strengthen the hypothesis that curtailing phase III would lower the capacity of current premarketing tests to identify adverse reactions. If the experiential data fail to detect the theoretical differences, then a better case can be made for curtailing phase III, with or without transfer of some of its testing to the postmarketing period.

Current interpretations of the statutory requirements for "adequate tests" of safety and "substantial evidence" of efficacy emphasize methodology, as reflected in the requirement that each indication for which a drug is intended be supported by at least two well-controlled clinical trials. But FDA can alter the criteria by which it approves drugs. For example, propanolol, the first beta-blocking drug approved for use in the United States, was approved by an advisory committee on the basis of all the evidence presented to FDA, even though no one study was found to be adequate and well controlled (21). And in late 1981, timolol, another beta-blocker, was approved, on the basis of evidence from a foreign study, for use in preventing death and recurrent heart attacks in patients who have survived initial heart attacks (26).

The approval of propanolol and timolol illustrates that FDA can grant exceptions to its usual requirement of two well-controlled U.S.-based clinical trials. In such cases, expert judgment relies on qualitative, not quantitative, criteria in approving a drug, and such an approach falls outside the theoretical and experiential guidelines outlined above. If FDA is to rely increasingly on such qualitative criteria through increased use of advisory committees, it will be necessary for FDA to develop general guidelines to aid the advisory committees in their deliberations. Otherwise, in a case-by-case analysis, evidence of the same quality may lead to approval for one drug and nonapproval for another.

Issue 2:

Improving postmarketing surveillance and its role in the drug approval process.

Even if phase III testing were not curtailed or eliminated, FDA's powers in the postmarketing period could be strengthened to enhance its surveillance role.

Postmarketing surveillance "systems" that have been advocated are not systems in the formal sense, but a series of related activities oriented toward several purposes, with the regulatory approval process being only one. Three activities are most frequently mentioned. First is the building of a resource base through training of additional experts and improving epidemiologic tools such as methods for cohort and case-control studies. Second, unless a drug effect has a sufficient fre-

quency of occurrence (usually identified as 1/1,000) and for delayed effects of, for example, greater than 1 year, strengthened voluntary reporting is the most realistic method of identifying possible adverse drug reactions. Once such reactions are suspected, clinical trials, case-control, and cohort studies could be used to determine whether an association with drug use in fact exists. Third is the development of an efficient method for monitoring selected drugs after their release into the market. The most frequently mentioned mechanism is formation of prospective cohorts of drug users.

These aforementioned components of a postmarketing surveillance "system" and FDA's role in supporting and using them are oversight issues.

There are also several legislative options that could strengthen FDA's powers in the postmarketing period. The following legislative options are presented for congressional consideration.

Option 1: Give FDA the power to require postmarketing studies.

A variation of this option is for FDA to use its existing regulatory powers over advertising and promotional practices to "certify" an industry-sponsored postmarketing study.

Option 2: Give FDA the power to restrict the distribution, dispensing, and administration of a drug.

A variation of this option is for FDA to use its existing regulatory powers to develop a parallel approval process for the use of a limited group of drugs during phase III testing, such as for drugs of unusual need and promise.

Option 3: Change the standard for a drug's removal from the market from "imminent hazard to the public health" to "unreasonable risk of illness to any segment of the population" or some other less stringent standard.

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Tab 49

TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PSYCHOPHARMACOLOGICAL AGENTS ADVISORY COMMITTEE

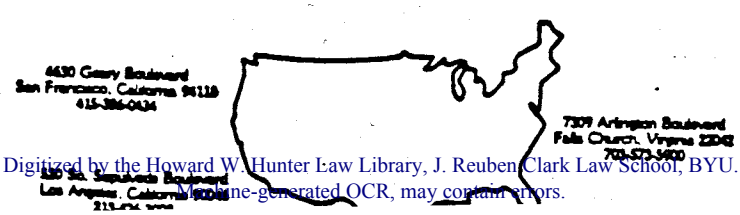
Date: March 22, 1977

Place: Rockville, Maryland

Pages: 240 - 323

SECOND DAY

BOWERS REPORTING COMPANY



kind of amnestic effect. This happens to me now and then with other drugs and there are rare times when the telephone rings in the night and I do not remember it, and it does not disturb me. So I really cannot become particularly concerned about those side effects. I agree that it would be well to monitor them more closely in the clinical studies that follow.

If I have any concerns or questions, I think there does need to be a restriction or warning against the use of this drug in the daytime -- it does not seem to be an anti-anxiety drug that one would want to take and drive an automobile or things like that. I am wondering if we have adequate studies in older individuals and I would ask Dr. Woo that.

DR. WOO: They have done some geriatric studies. In the geriatric, the dose cannot go beyond .5 -- they never gave it beyond .5.

DR. OVERALL: It would seem to me a drug of this sedative potency -- it might be particularly important to have some concern about the older individuals, and apart from that I really have no concerns about it and I am actually extremely impressed with the amount of work that has been done, the high potency and the short half-life of this compound.

DR. UHLENHUTH: I would also just like to take this opportunity to compliment the company on the job they have done. It seems to me that the quantity and quality of the data addressing the general question is really outstanding.

in addiction-prone individuals as for all hypnotics and prescriptions should be limited to those patients who are under medical supervision.

DR. ENDICOTT: Yes, but that does not meet my concern that there be a warning that it is easier to overdose, or some indication that the therapeutic dose and the overdose dosage are relatively close, and patients should be discouraged from taking more than some upper limit.

DR. HAYES: In regard to my cursory review, the things I thought needed attention are the scheduling, which will be considered by the committee, the basis of which Dr. Kennedy has given you his early appraisal, and some revisions in the package insert which I think we would be willing to consider when that as well as other bits of data are finally evaluated. But other than I do not have anything.

DR. KORNETSKY: At the present time we have not concerned ourselves with the specifics of the package insert.

DR. SCHIELE: The question is whether the drug is approvable or not, and the package insert details would be hammered out.

DR. KORNETSKY: Let me just ask one question regarding page 461. It says -- physical and psychological dependence have not occurred in patients taking .5 milligrams per day for 90 days or in normal human volunteers taking one milligram per day for 42 days. How does that fit with the material that

Tab 50

SGG

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE

Thirty-First Meeting

Volume II

9:00 a.m.

Friday, September 22, 1989

Plaza I
Crowne Plaza Hotel
1750 Rockville Pike
Rockville, Maryland

MILLER REPORTING CO., INC.
507 C S[illegible], N.E.
Washington, D.C. 20002

basically for certain information. We get information about the patient. We get information about the drug that is suspected. We get information about the reaction and we get information about other relevant medical features and other drugs. We also can contact the firm or the physician and get additional information if that is deemed necessary.

But what I am going to tell you about is a system of analysis which computerizes these forms. We have a standardized way of taking the information on the 1639 form and computerizing it. We currently have 450,000 reports in our computer file. We put 50,000 reports in every year. We get the reports in within 1 week of receipt within the Food and Drug Administration. So this is a current system that we are dealing with. There is no backlog.

(Slide)

The reports come from any of these sources. They may go from the physician or nurse to the manufacturer to the FDA or they may come directly to FDA.

(Slide)

When we look at our entire system, we see that 90 percent of the reports come from the manufacturer. That is, they come indirectly to the manufacturer and to us. When we look at the data we are going to look at today, we see roughly the same proportions. We know that health professionals provide only about 10 percent of the reports directly

Tab 51

Summary Basis of Approval

NDA 18-163

Drug Generic Name: temazepam

Trade Name: Restoril

Applicant:
Sandoz Pharmaceuticals
East Hanover, New Jersey 07936

I. Indications for Use:

Restoril[R] (temazepam) is indicated for the relief of insomnia associated with the complaints of difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Although clinical studies show effects on sleep induction, sleep laboratory studies have not confirmed a reduction in sleep latency when the drug was administered within thirty minutes of retiring.

Since insomnia is often transient and intermittent, the prolonged administration of Restoril[R] is generally not necessary or recommended. Restoril has been employed for sleep maintenance for up to 35 consecutive nights of drug administration in sleep laboratory studies.

II. Dosage Form, Dosage, and Administration:

Oral Capsules, 15 and 30 mg, one of either strength before retiring.

III. Manufacturing and Controls:

A. Finished dosage form is adequately controlled by suitable methodology: IR, dissolution g.c., manufacturing processing is adequately described.

B. Stability studies: 5 years stability is established by appropriate methodology: TLC, differential polarography.

C. Method Validation: Has been satisfactorily completed in May, 1979 (Chicago District Laboratories) and the revised dissolution methodology has been satisfactorily validated in October, 1980.

D. Labeling: Labeling is technically satisfactory.

E. Establishment Impact Analysis: No adverse environmental effect will occur.

F. Establishment Inspection: EIR 11/3/79, profile 12/24/80

IV. Pharmacology:

A. Temazepam is a benzodiazepine derivative that differs structurally from diazepam only by a hydroxyl at the 3-position of the diazepine ring and from oxazepam by a methyl group at the 1-position of the diazepine ring.

B. Sandoz has submitted toxicity/carcinogenicity studies in mice at 10, 80 and 160 mg/kg/day and in rats at 10, 40, 160 mg/kg/day (equivalent to 20, 80, 320 times the recommended human dose) as well as a chronic toxicity study in dogs at 15, 45, and 135 mg/kg/day. Mice receiving the highest dose had increased incidences of hyperplastic liver nodules and telangiectasis compared to controls. Rats ingesting the high dose exhibited hepatocellular hypertrophy with cytoplasmic lipidosis and a somewhat higher incidence and enhanced severity of kidney pathology including epithelial hyperplasia and cortical cysts. Esophageal distention also occurred in some high dose rats. Although mortality was greater relative to controls in all treated males and in females receiving the low dose, a causal relationship of drug treatment to mortality is doubtful because of the lack of dose response and the absence of consistent toxicity in the lower dosage groups. The incidence of total or specific tumors was not increased in mice or rats after long term temazepam treatment. All dogs receiving temazepam in the 1 year study showed dose-related uncoordination but no consistent toxicity or organ pathology that could be associated with drug treatment. Reproduction studies were conducted in rats and rabbits. In a perinatal-postnatal study (segment III) in rats doses of 60 and 120 mg/kg/day but not 30 mg/kg/day resulted in higher nursing deaths. Teratology studies in rats demonstrated increased fetal resorptions at doses of 30 and 120 mg/kg/day and an increased incidence of rudimentary ribs, which are considered skeletal varients, at doses of 240 mg/kg or higher. In pregnant rabbits doses of 40 mg/kg/day resulted in the increased occurrance of rudimentary 13th ribs. No major fetal malformations were seen in any study that could be attributed to temazepam treatment.

Drug metabolism studies with temazepam in mice, rats, dogs, and man showed that conjugated temazepam and conjugated oxazepam were the two principal urinary metabolites. Studies in absorption and excretion of temazepam in man indicated that the drug is well absorbed through the GI tract. Peak plasma levels were reached within 2-3 hours and declined with biphasic T half values of 0.6 and 9 hours. Similar absorption, time to peak plasma levels and plasma T half life were found in mice, rats and dogs. When temazepam was given to pregnant rats, temazepam and its metabolites were found in the fetus and also detected in the mother's milk.

C. The relevant toxicities in rodents after chronic treatment with high doses of temazepam involve liver changes of hypertrophy, lipidosis, and hyperplasia and kidney pathology including enhanced nephritis, epithelial hyperplasia and cortical cysts. The firm has recommended in the event of repeated temazepam use in patients that liver and kidney function tests be performed and that the usual precautions should be observed in patients with impaired renal or hepatic function.

V. Medical Portion:

A. Restoril is a 1, 4-benzodiazepine structurally related to marketed benzodiazepines such as flurazepam, diazepam, oxazepam, and chlordiazepam. The clinical efficacy of temazepam as a hypnotic was demonstrated in double blind studies involving 508 adult patients. Most of the clinical studies used subjective methodology, i.e. patient and physician questionnaires and simple numerical rating scales. A sleep laboratory setting was used for 3 other clinical studies.

B. Substantial efficacy was shown by three major subjective clinical trials and one objective study (sleep lab). The following parameters were measured in all subjective studies contained in the NDA:

(1) sleep induction
(2) frequency of nocturnal awakenings
(3) sleep duration
(4) effect on early morning awakenings
(5) quality of sleep
(6) residual effects of medication noted the following morning
(7) patients general opinion of the study medication compared to previous sleep medications used
(8) physicians' global evaluation of patients' responses

Pivotal Clinical studies for efficacy and safety proof - Heffron, Rosen, Fillingim, Dement.

(1) Heffron study - 55 outpatients aged 18-59, males and females with chronic insomnia for at least one year. Double blind placebo controlled parallel groups. Temazepam was significantly better than placebo ($p = 0.05$) in five of five measured parameters: sleep induction, nocturnal awakenings, sleep duration, early morning awakenings and sleep quality. The study length was four consecutive nights using the 30 mg dosage. Drowsiness and fatigue occurred frequently and were of a mild degree.

(2) Rosen study - 82 adult outpatients age 18-59, double blind placebo control, comparison group using 30 mg. Dalmane. Diagnosis - chronic insomnia for at least one year. Temazepam was significantly better than placebo in three of five parameters: nocturnal awakenings, early morning awakenings, and sleep quality. The efficacy pattern was similar to that of the Dalmane group. No safety problems occurred in the study.

(3) Fillingim study - 75 adult outpatients with chronic insomnia of at least one year, ages 18-59. Double blind placebo controlled with a third group taking 500 mg Doriden per day, duration 4 consecutive nights. 30 mg temazepam was significantly more effective (p 0.05) than placebo in five of five parameters: sleep induction, nocturnal awakenings, sleep duration, early morning awakenings, and sleep quality. Its efficacy profile paralleled that of 500 mg Doriden in all parameters.

(4) Dement study - method continuous nightly monitoring of sleep pattern and sleep stages in a sleep laboratory. 8 adult patients were studied for at least 6 wks. and had to meet strict sleep lab confirmed entry criteria for the study. The study consisted of placebo nights, analyzed nights with active drug, and a recovery period using placebo for each dosage. Temazepam in both dosages showed statistically significant increases in total sleep time and significant reductions in wake time after sleep onset. No significant withdrawal effects were noted after administration of 30 mg temazepam for 35 consecutive nights.

C. Many other well controlled studies were supportive of efficacy of the 30 mg dosage in all age groups from age 18-96, both outpatients and hospitalized. The Dement study was the only study showing a hypnotic effect for the 15 mg dosage, other studies showing favorable trends but not reaching statistical significance.

Two other sleep laboratory studies were performed. The Vogel study utilized 23 consecutive drug nights followed by an eleven night placebo (drug withdrawal) period. Temazepam significantly increased total sleep time and significantly decreased both the number of awakenings and the total wake time; the drug had no effect on sleep latency in this study. Each of the six insomnia measures was tested for insomnia during withdrawal; total sleep time was significantly less during post-drug nights one through three, and this effect was principally due to the values for the first drug withdrawal night. In the Kales study, six patients received temazepam from night 8 through night 35 with placebo for the preceeding (baseline) week and during two weeks following drug discontinuance. The number of nocturnal awakenings was significantly decreased, but sleep latency and total wake time after sleep onset were not significantly changed from baseline values. When the three sleep laboratory studies were reanalyzed using non-parametric techniques, there was no statistically significant median decrease from baseline for sleep latency (over the entire treatment period) for any of the three studies, and for the Kales study there was a significant median increase. With regard to sleep disturbances following withdrawal, the three studies did not follow a consistent pattern. For the Dement and Vogel studies, both sleep latency and total sleep time had large median deteriorations from baseline during the first withdrawal

period, and these deteriorations disappeared during the second withdrawal period. In the Kales study, there were small median deteriorations during the first withdrawal period which became larger during the second withdrawal period.

Phase I studies in normal volunteers showed the drug to be well tolerated in single daily dosages up to 90 mg/day. Beyond this level significant increases in standing pulse rates appeared. Drowsiness and fatigue were common effects in all subjects. EKG's, eye examinations, clinical laboratory tests, and vital signs did not deviate significantly.

D. Safety evaluations were conducted in all of the clinical studies in the NDA, the duration of treatment being 4 consecutive nights except in the 35 night sleep lab study by Dement. A long term safety study using double blind parallel groups was conducted in 82 adult outpatients age 18-65 using 30 mg Dalmane for comparison, both drugs being given daily for 12 weeks Evaluations of laboratory tests including liver and kidney function showed no significant deviations during the treatment period. No liver enzyme induction occurred in this 12 week study. EKG's and eye examinations remain normal throughout.

The pattern of occasional transient laboratory abnormalities, e.g. slight SGOT rises, was noted in all of the 4 day efficacy studies. Their occurences were transient and mild, occurring at the same rates in drug and placebo groups. Adverse reactions which occurred in all studies were rated as mild except for a few instances of severe drowsiness and fatigue. In most studies there were no significant differences in occurence rates between drug groups and placebo groups. The overall frequency for adverse reactions in all clinical studies (795 patients) including tolerance studies was: drowsiness (17%), dizziness (7%), and lethargy (5%). Other side effects included confusion (2-3%) and weakness (1-2%). Rarely reported were tremor, ataxia, lack of concentration, loss of equilibrium, falling and palpitations (less than 1%).

E. The final draft of the new drug labeling was reviewed and found to be adequate and complete.

IV. Copy of package insert attached.

T A Hayes

Thomas A. Hayes, M.D.
Group Leader

Joyce Creamer

Joyce Creamer
Consumer Safety Officer

Doc#1021A

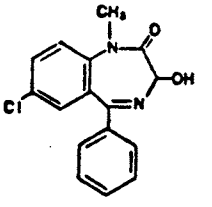
RESTORIL®
(temazepam)
Capsules

CAUTION: Federal law prohibits dispensing without prescription

WORKING COPY
compared
DRAFT and ltr. 1-29-81.

DESCRIPTION

Restoril® (temazepam) is a benzodiazepine hypnotic agent. The chemical name is 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, and the structural formula is:



Temazepam is a white, crystalline substance, very slightly soluble in water and sparingly soluble in alcohol USP. It has a molecular weight of 300.7.

Restoril (temazepam) capsules, 15 mg and 30 mg, are for oral administration.

CLINICAL PHARMACOLOGY

Restoril (temazepam) improved sleep parameters in clinical studies in patients with a clinical diagnosis of insomnia characterized by difficulty falling asleep, frequent awakenings, a particular problem in the geriatric patient, was significantly reduced.

In sleep laboratory studies, Restoril (temazepam) significantly improved sleep maintenance parameters (fewer wake time after sleep onset, total sleep time and the number of nocturnal awakenings). There was no significant reduction in sleep latency. REM sleep was essentially unchanged, slow wave sleep was decreased and no rebound effects occurred in these sleep stages. Transient sleep disturbance, mainly during the first night, occurred after withdrawal of the drug. In these studies, there was no evidence of tolerance when patients were given Restoril nightly for approximately one month.

A single and a multiple dose absorption, distribution, metabolism and excretion (ADME) study using ^{14}C-labeled drug, as well as a bioavailability study, were carried out in normal volunteers. Absorption was complete and detectable blood levels were achieved at 20-40 minutes; peak concentration was reached at 2-3 hours. There was minimal (approximately 8%) first pass metabolism.

The only significant metabolite present in blood was the O-conjugate. The unchanged drug was 96% bound to plasma proteins. The blood level decline of the parent drug was biphasic with the short half-life ranging from

Following abrupt discontinuance of benzodiazepines, withdrawal symptoms similar in character to those noted following withdrawal of barbiturates and alcohol have occurred. [illegible] be exercised in administering Restoril (temazepam) to individuals known to be addiction-prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeated prescriptions without adequate medical supervision.

OVERDOSAGE

Manifestations of acute overdosage of Restoril (temazepam) can be expected to reflect the CNS effects of the drug and include somnolence, confusion and coma, with reduced or absent reflexes, respiratory depression and hypotension. If the patient is conscious, vomiting should be induced mechanically or with emetics. Gastric lavage should be employed utilizing concurrently a cuffed endotracheal tube if the patient is unconscious to prevent aspiration and pulmonary complications. Maintenance of adequate pulmonary ventilation is essential. The use of pressor agents intravenously may be necessary to combat hypotension. Fluids should be administered intravenously to encourage diuresis. The value of dialysis has not been determined. If excitation occurs, barbiturates should not be used. It should be borne in mind that multiple agents may have been ingested.

The oral LD_{50} was 1963 mg/kg in mice, 1833 mg/kg in rats and >2400 mg/kg in rabbits.

DOSAGE AND ADMINISTRATION

The recommended usual adult dose is 30 mg before retiring. In some patients, 15 mg may be sufficient. As with all medications, dosage should be individualized for maximal beneficial effects. In elderly and/or debilitated patients it is recommended that therapy be initiated with 15 mg until individual responses are determined.

HOW SUPPLIED

Restoril (temazepam) capsules–15 mg, maroon and pink, imprinted "RESTORIL 15"; 30 mg, maroon and blue, imprinted "RESTORIL 30". Packages of 100, 500 and ControlPak® packages of 25 capsules (continuous reverse-numbered roll of sealed blisters).

SANDOZ PHARMACEUTICALS
Division of Sandoz, Inc.
East Hanover, N.J. 07936

FEBRUARY 4, 1981 PRINTED IN U.S.A.

4-0.6 hours and the terminal half-life from 9.5-12.4 hours (mean 10 hours), depending on the study population and method of determination. Metabolites were formed with a half-life of 10 hours and excreted with a half-life of approximately 2 hours. Thus, formation of the major metabolite is the rate limiting step in the biodisposition of temazepam. There is no accumulation of metabolites. The area under the blood concentration-time curve was directly proportional to the dose in the 0-45 mg range.

Temazepam was completely metabolized prior to excretion. 80-90% of the dose appeared in the urine. The major metabolite was the O-conjugate of temazepam (88%); the O-conjugate of N-demethyl temazepam was a minor metabolite (7%). There were no active metabolites.

At a dose of 30 mg once-a-day for 8 weeks, no evidence of enzyme induction was found in man.

The steady state plasma concentration measured under therapeutic sleep laboratory conditions was 382 ± 192 ng/ml, 2.5 hours after a 30 mg dose, and 26 ng/ml at 24 hours. On a once-a-day regimen, steady state was attained on the third day.

INDICATIONS AND USAGE

Restoril (temazepam) is indicated for the relief of insomnia associated with the complaints of difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. In clinical trials there is a perception by patients that Restoril (temazepam) decreases sleep latency, but sleep laboratory studies have not confirmed such an effect when the drug was administered within 30 minutes of retiring.

Since insomnia is often transient and intermittent, the prolonged administration of Restoril (temazepam) is generally not necessary or recommended. Restoril (temazepam) has been employed for sleep maintenance for up to 35 consecutive nights of drug administration in sleep laboratory studies.

[illegible] several organic disorders. It is possible that the complaint may be related to a condition for which there is more specific treatment should be considered.

CONTRAINDICATIONS

Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Transplacental distribution has resulted in neonatal CNS depression following the ingestion of therapeutic doses of a benzodiazepine hypnotic during the last weeks of pregnancy.

Reproduction studies in animals with temazepam were performed in rats and rabbits. In a perinatal-postnatal study in rats, oral doses of 60 mg/kg/day resulted in increasing nursling mortality. Teratology studies in rats demonstrated increased fetal resorptions at doses of 30 and 120 mg/kg in one study and increased occurence of rudimentary ribs, which are considered skeletal variants, in a second study at doses of 240 mg/kg or higher. In rabbits, occasional abnormalities such as exencephaly and fusion or asymmetry of ribs were reported without dose relationship. Although these abnormalities were not found in the concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg or higher, there was an increased incidence of the 13th rib variant when compared to the incidence in concurrent and historical controls.

Restoril (temazepam) is contraindicated in pregnant women. If there is a likelihood of the patient becoming pregnant while receiving temazepam, she should be warned of the potential risk to the fetus. Patients should be instructed to discontinue the drug prior to becoming pregnant. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered.

PRECAUTIONS

General

Since the risk of the development of oversedation, dizziness, confusion and/or ataxia increases substantially with larger doses of benzodiazepines in elderly and debilitated patients, 15 mg of Restoril® (temazepam) is recommended as the initial dosage for such patients.

Restoril (temazepam) should be administered with caution in severely depressed patients or those in whom there is any evidence of latent depression; it should be recognized that suicidal tendencies may be present and protective measures may be necessary.

If Restoril (temazepam) is to be combined with other drugs having known hypnotic properties or CNS-depressant effects, consideration should be given to potential additive effects.

Information for Patients

Patients receiving Restoril (temazepam) should be cautioned about possible combined effects with alcohol and other CNS depressants. Patients should be cautioned not to operate machinery or drive a motor vehicle after ingesting the drug. Patients should also be advised that they may experience disturbed nocturnal sleep for the first or second night after discontinuing the drug.

Laboratory Tests

The usual precautions should be observed in patients with impaired renal or hepatic function. Abnormal liver function tests as well as blood dyscrasias have been reported with benzodiazepines.

Carcinogenesis, Impairment of Fertility

No carcinogenic potential was demonstrated in long-term studies in mice and rats. Fertility in male and female rats was not adversely affected by Restoril (temazepam).

Pregnancy

Pregnancy Category X. See Contraindications.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Restoril (temazepam) is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS

During clinical studies in which 795 patients received Restoril (temazepam), the drug was well tolerated. Side effects were usually mild and transient. These 795 patients included 175 subjects who received Restoril (temazepam) during daytime waking hours, sometimes in excess of recommended therapeutic dosage, in studies to evaluate dosage levels for safety and pharmacokinetic profiles.

The most common adverse reactions were drowsiness (17%), dizziness (7%), and lethargy (5%).

Other side effects include confusion, euphoria and relaxed feeling (2-3%). Less commonly reported were weakness, anorexia and diarrhea (1-2%). Rarely reported were tremor, ataxia, lack of concentration, loss of equilibrium, falling and palpitations (less than 1%).

Hallucinations, horizontal nystagmus and paradoxical reactions, including excitement, stimulation and hyperactivity were rare (less than 0.5%).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Restoril (temazepam) is a controlled substance in Schedule IV.

Abuse and Dependence

Withdrawal symptoms following abrupt discontinuation of benzodiazepines have been reported in patients receiving relatively high doses over extended periods of time. These symptoms, including convulsions, are similar to those seen after barbiturate withdrawal. Although infrequently seen milder withdrawal symptoms have also been reported

Tab 52

Report of the Tort Policy Working Group on the Causes, Extent and Policy Implications of the Current Crisis in Insurance Availability and Affordability

February 1986

TABLE OF CONTENTS

INTRODUCTION

AND

EXECUTIVE SUMMARY

In October of last year the Attorney General established the Tort Policy Working Group, an inter-agency working group consisting of representatives of ten agencies and the White House. One of the tasks the Working Group was asked to undertake was to examine the rapidly expanding crisis in liability insurance availability and affordability.

The following is the report of the Tort Policy Working Group on the causes, extent and policy implications of this crisis. The primary contributing agencies included the Department of Justice, the Department of Commerce and the Small Business Administration.

Chapter 1 of the report (The Crisis in Insurance Availability and Affordability) describes in detail the significant problems many businesses, professionals and municipalities are having obtaining liability insurance. The Chapter documents a dramatic change in the last two years in the availability, affordability and adequacy of liability insurance. Where insurance is available (and in some areas it simply is not), premium increases of several hundred percent over the last year or two have become commonplace. Few if any private or public entities that rely on liability insurance have escaped the problems generated by this crisis.

Part A of Chapter 2 (The Causes of the Crisis in Insurance Availability and Affordability) reviews the current financial condition of the insurance industry, and the economic factors leading to that condition. The property-casualty industry in the past two years has suffered significant underwriting losses ($21 billion in 1984; $25 billion in 1985) which have limited its ability to offer as much insurance as its customers desire, and have made it reluctant to insure high risk activities which may expose it to further substantial underwriting losses. These underwriting losses appear to be largely a result of coverage written in the late 1970's and early 1980's which may have been underpriced due to the industry's desire to obtain premium income to invest at the then prevailing high interest rates.

Nonetheless, there is little to suggest that the recent massive increases in premiums is related solely to these losses, or that the cost of liability insurance will decline significantly as the industry limits its underwriting losses and restores its desired level of overall profitability. To the contrary,

indications are that developments in tort law are a major cause for the sharp premium increases. 1/

Part B of Chapter 2 reviews the contribution of tort law to the insurance availability/affordability crisis. The Working Group found that in the past decade there has been a veritable explosion of tort liability in the United States. Four specific problem areas are identified and discussed:

- The movement toward no-fault liability, which increasingly results in companies and individuals being found liable even in the absence of any wrongdoing on their part.

- The undermining of causation through a variety of questionable practices and doctrines which shift liability to "deep pocket" defendants even though they did not cause the underlying injury or had only a limited or tangential involvement.

- The explosive growth in the damages awarded in tort lawsuits, particularly with regard to non-economic awards such as pain and suffering or punitive damages. And,

- The excessive transaction costs of the tort system, in which virtually two-thirds of every dollar paid out through the system is lost to attorneys' fees and litigation expenses.

The Working Group was particularly struck by the extraordinary growth over the last decade of the number of tort lawsuits and the average award per lawsuit. A few examples amply illustrate this point:

- Between 1974 and 1985 there has been a 758% increase in the number of product liability lawsuits filed in federal district court.

- The number of medical malpractice lawsuits per 100 physicians doubled between 1979 and 1983, and tripled during that period for obstetricians/gynecologists.

- According to a jury verdict reporting service, between 1975 and 1985 the average medical malpractice jury

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1/ The Working Group also considered whether state regulation of the insurance industry may be a cause of the crisis, and found little compelling evidence that state regulation is a major cause of these problems.

verdict increased from $220,018 to $1,017,716, and the average product liability jury verdict increased from $393,580 to $1,850,452. 2/

- A survey of punitive damage awards in Cook County, Illinois indicates that the average personal injury punitive damage award (measured in constant 1984 dollars) increased from $40,000 in 1970-74 to $1,152,174 in 1980-84.

The above data demonstrates that the insurance industry was selling coverage at constant or even reduced cost over a period of years during which tort liability was undergoing a dramatic expansion. This suggests that a major factor underlying the availability/affordability crisis is the industry's attempt to bring premiums quickly back into line with rapidly growing liability risks. 3/ The high -- and in some areas unaffordable -- insurance premiums reflect the fact that tort law is now placing a massive compensation burden on the private sector.

A second important contribution of tort liability to the availability/affordability crisis is the tremendous uncertainty that has been generated by rapidly changing standards of liability and causation. The "rules of the game" have become so unpredictable that the insurance industry often cannot assess liability risks with any degree of confidence. This appears to have severely exacerbated the problem.

Chapter 3 of the report (Recent Insurance Industry Developments) summarizes a number of responses of the insurance industry, its customers and state regulators to the crisis. These developments include the use of claims-made policies, the inclusion within policy limits of all or part of defense costs, the increasing use of self-insurance and captives, and more exacting state regulation.

In Chapter 4 of the report (Tort Law Reform) the Working Group concludes that while some of the above recent developments in the insurance industry, along with a likely improvement in the industry's financial condition, should relieve some of the current availability/affordability problems, it is unlikely that these changes will provide long-term, systemic relief without

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2/ For purposes of comparison, the dollar lost approximately half of its purchasing power during this period.

3/ While some have suggested that the dramatic premium increases are an attempt by the industry to recoup its past underwriting losses, for the reasons discussed in the report such a theory makes little economic sense.

some fundamental reforms of tort law. Indeed, there are good reasons to believe that absent such reforms, particularly the insurance affordability problem will remain a long-term fixture of the American economy.

The Working Group recommends eight reforms of tort law that should significantly alleviate the crisis in insurance availability and affordability. The Working Group does not at this time recommend how these reforms should be implemented (whether at the federal or state level, or through legislative or judicial modification of the law); nor are these reforms meant to be an exhaustive list of potential reforms. The recommended reforms are:

- Return to a fault-based standard for liability.
- Base causation findings on credible scientific and medical evidence and opinions.
- Eliminate joint and several liability in cases where defendants have not acted in concert.
- Limit non-economic damages (such as pain and suffering, mental anguish, or punitive damages) to a fair and reasonable maximum dollar amount.
- Provide for periodic (instead of lump-sum) payments of damages for future medical care or lost income.
- Reduce awards in cases where a plaintiff can be compensated by certain collateral sources to prevent a windfall double recovery.
- Limit attorneys' contingency fees to reasonable amounts on a "sliding scale."
- Encourage use of alternative dispute resolution mechanisms to resolve cases out of court.

Chapter 5 of the report (Government Insurance: A Non-Solution) details the reasons why government insurance or indemnification would be highly undesirable and would do nothing to remedy the problems underlying the availability/affordability crisis. Such a federal insurance or indemnification program would not only be extremely expensive, but also could exacerbate the problems of tort law by making the "deep pocket" of the taxpayer available in many cases. In addition, such a program could undermine public health and safety, require more extensive government regulation of private sector activities, involve the government in substantial litigation, lead to increased federal involvement in state insurance regulation, and inhibit the ability of the private sector to adapt insurance services to changing economic and social conditions.

The Conclusion to the report lists five conclusions as to the appropriate response of the federal government to the current crisis in insurance availability and affordability. In sum, the Working Group concludes that while there are a number of factors underlying the insurance availability/affordability crisis, tort law is a major cause which the federal government can address in various sensible and appropriate ways. As for some of the other factors underlying the crisis, such as the insurance industry's recent large underwriting losses, there is little the federal government can or should do to remedy these problems.

In that both the tort liability and insurance developments in this report are highly dynamic, and because more detailed data and other studies undoubtedly will become available, the Working Group will continue to follow developments in this area, and, where appropriate, supplement its conclusions and recommendations.

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CHAPTER 1

THE CRISIS IN INSURANCE AVAILABILITY AND AFFORDABILITY

Liability insurance is a linchpin in the operation of the United States economy, yet many American businesses, professionals and municipalities, both large and small, are encountering serious insurance problems arising from premium increases, policy cancellations and refusals to underwrite certain activities.

The liability insurance crisis has three separate but related faces that individually or in various combinations make it difficult for many entities to obtain the desired liability insurance. These problems are availability of insurance, affordability of insurance coverage and adequacy of coverage.

This Chapter describes the current nature and extent of these problems. The Chapter focuses, first, on the problems encountered within the various lines of insurance, and, second, on the effect of those problems on different sectors of the economy.

I. INSURANCE COVERAGE SUMMARIES

The following are insurance summaries taken predominantly from insurance industry reports prepared by the Alliance of American Insurers or published in Business Insurance.

Environmental Impairment Liability Insurance ("EIL")

EIL covers pollution incidents stemming from gradual pollution exposures (as opposed to "sudden and accidental" pollution, which traditionally has been covered under general liability coverage). Two major companies dropped out of the market in 1985, and by the end of the year only two companies were offering EIL coverage. Forty-seven companies were forced to close hazardous-waste management facilities for lack of EIL coverage. Most hazardous waste businesses currently are looking toward captives and self-insurance. Brokers expect significant price increases on the limited insurance still available.

Sudden and Accidental Pollution Coverage

Coverage for sudden and accidental pollution traditionally has been provided as part of general liability coverage. New general liability forms, however, specifically exclude all pollution liability. This is due to court decisions interpreting "sudden and accidental" coverage as also covering gradual and intentional pollution. (See Chapter 3 for a discussion of the new policy forms.) The London market currently is excluding pollution coverage from the large risks it insures.

Directors and Officers Liability ("D & O")

Premiums in 1985 rose 50% to 500%, and include larger deductibles, lower limits, more restrictive endorsements and shorter policy durations. Industries particularly affected include financial institutions, electric (nuclear) utilities, new high technology business, wildcat oil and gas companies, research and development enterprises, real estate developers, highly leveraged businesses, petrochemical companies and the steel industry. Capacity constrictions have hurt larger risks more than smaller risks. Traditional primary and reinsurance capacity has been reduced, but Lloyd's of London, which has in the past not been active in this line, is offering primary coverage up to $20 million. Not surprisingly, business with Lloyd's of London is up to 100% to 200%. Much of the reinsurance market for such coverage has virtually dried up.

Bank Fidelity Bond Coverage

Premiums are up about 300%. A group of fifty banks are creating a mutual insurer to provide D & O and bankers blanket bond coverage.

Motor Carrier Liability Coverage

Bus and trucking companies are having severe difficulties obtaining the insurance coverage required by federal law. The Motor Carrier Act of 1980 requires insurance minimums of from $750,000 for carriers of non-hazardous cargo to $5 million for carriers of hazardous waste and most hazardous materials carried in bulk. The Bus Regulatory Reform Act of 1982 set insurance minimums from $1.5 million to $5 million, depending on the passenger capacity of the bus. Capacity is limited both in the primary and reinsurance markets. Small trucking firms and independent owner-operators have the most difficulty getting insurance.

Liquor Liability Coverage

Liquor liability coverage may be available as part of a commercial lines package, but is severely constrained and virtually nonexistent in some parts of the country as monoline coverage. This line has been affected by the bankruptcy of one of the largest dram shop insurers, Ideal Mutual Insurance Company.

Medical Malpractice Insurance

Availability problems are being encountered by nurse/midwives, obstetricians/gynecologists, pediatricians and dentists. Premiums are being raised and coverage limits are being reduced, sometimes by as much as 50%. Reinsurers are also restricting coverage in this line. St. Paul's Insurance Company, the largest medical malpractice insurer, has placed a moratorium on new policies. St. Paul's writes coverage for approximately 20%

of the Nation's doctors, and wrote an estimated $600 million in malpractice business in 1985. It had a pure loss ratio (excluding loss adjustment expenses and operating expenses) of 81.3% in 1984. Doctor-owned mutual insurance companies account for more than half of the medical liability coverage in the country.

Commercial General Liability ("CGL")

Commercial general liability insurance has undergone significant premium increases. The Insurance Services Office ("ISO"), the property-casualty insurers' statistical and ratemaking organization, has filed a new CGL form which will limit coverage and which contains certain exclusions and policy limitations (see Chapter 3).

Excess Coverage

Excess coverage capacity has been sharply reduced. This coverage currently is offered primarily on a claims-made basis, which may or may not mesh with the primary, reinsurance and other excess layers.

Reinsurance

Reinsurance capacity for the United States market has been severely limited, particularly with regard to Lloyd's of London, which has faced both its own problems and a disillusionment with the American market. This capacity problem is expected to ease somewhat in 1986, but is likely to remain a problem for some time longer.

II. SECTORAL SUMMARIES

The following are summaries of the effect of the insurance availability/affordability crisis on various sectors of the United States economy. This information was obtained from surveys conducted by business groups, articles in the trade press and materials prepared by trade associations or provided by industry representatives. While the following does not include all of the available information, it summarizes the major findings.

Municipalities

Municipalities are among the hardest hit groups by both affordability and availability problems. Local officials preparing their budgets for the next fiscal year report that the market for public entities is "extremely limited" and "diminishing to nothing." Those cities able to secure bids are finding insurance companies' offers prohibitively expensive. Renewal rates have climbed by as much as 400% -- and often for lower coverages with higher deductibles. Some cities are facing premium increases of up to 1,000%.

The United States Conference of Mayors conducted a survey of 39 cities in the summer of 1985. Over half the cities were quoted premium increases of over 100%, and 16 were quoted increases greater than 200%. In addition, a recent report by the Wyatt Company, Public Officials Liability Insurance: Understanding the Market (1986), notes that local governments have reported premium increases of 200% to 300% in the insurance purchased for their officials.

Rather than renew, many cities have decided to "go bare." All cities have been forced to reevaluate and sometimes limit the services they provide their communities. Finally, in the wake of policy cancellations, a number of city and county officials have resigned, fearing personal exposure to lawsuits stemming from their official duties.

Transportation

The American Public Transit Association, the nation's largest organization of transit operators, reports that premiums for those companies able to obtain insurance this year have gone up 500% to 1,000%, and sometimes more. In Los Angeles, the Southern California Rapid Transit District's annual premium jumped from $67,000 to $1.7 million, while coverage was reduced. Transit problems were compounded by the bankruptcy of one of the largest companies involved in insuring mass transit systems. Some local transit systems have had to suspend operations.

Publishing

Newspaper and magazine publishers are finding it more difficult to obtain libel insurance.

Nurse-Midwives

The American College of Nurse-Midwives represents 2,500 members, 1,400 of whom were covered under a blanket policy through the association. The policy was cancelled on July 1, 1985. The association has been unable to obtain other coverage and has been attempting to create a captive insurer. The captive was to have started operation by April 1, 1986, but that deadline will not be met.

Grocers

A survey by the National Grocers Association found that its members' liability insurance premium rates had recently increased from 25% to 500%. The survey covered 161 retailers and 20 wholesalers.

Architects and Engineers

Most architectural and engineering firms, and particularly smaller firms, are experiencing severe availability and affordability problems. Insurance premium rate increases of

200% to 300% have become the norm. Roughly 30% to 40% of smaller firms are going bare. Engineering firms involved in asbestos or other toxic substances abatement activities face extreme difficulties in obtaining insurance, with rate increases, where insurance is available, of 5,000% not uncommon.

Day Care Centers

The National Association for Education of Young Children conducted a survey of day care providers. They covered family day care providers who care for children in a home setting, day care centers and headstart programs. The survey found that 40% of the respondents had had their insurance cancelled or not renewed and the majority of those with coverage had premium increases, most of which rose 200% to 300%.

Toy Manufacturers

The Toy Manufacturers of America recently surveyed its 243 members on insurance cost and availability problems. Final results will not be available until April, but initial responses are:

Members	%Increase in premiums
21	50
9	50-100
12	100-150
2	150-200
11	300-500
7	500-1000
1	over-1000
2	cannot obtain insurance

Companies that normally had three to four months to negotiate a policy renewal have been given only 72 hours to do so this year. This permits insufficient time for policy shopping. The association reports that it had recommended a captive to its members a few years ago. Commercial insurers reduced prices upon learning of the proposal, eliminating industry interest in a captive.

Household Appliance Manufacturers

The household appliance industry has seen sharp reductions in available coverage, and the Association of Home Appliance Manufacturers has lost group coverage it had arranged in 1983. Many companies have been able to obtain only about one-third of the coverage sought for product liability, and the cost of that coverage is increasing. Member companies are having similar problems obtaining D & O insurance.

Automobile Repair

The Automotive Services Councils, an association representing automobile repair shops and garages, conducted a survey with 104 responses. Average premium increases were 70% to 80%. Some 13% of the membership reported purchasing an average of 30% less coverage. Approximately 41% had experienced policy cancellations and 26% were unable to find new carriers.

Medical Equipment

The medical equipment industry has had a captive, MedMarc, an affiliate of the Health Industry Manufacturers Association, since 1979. The captive started with 35 companies and has recently reached 100 member companies. The rate of growth increased in 1985 as the result of cancellations by commercial insurers of about 20% of the Association's members and premium increases of five to ten-fold.

Biotechnology

Biotechnology companies are having a particularly difficult time in the tight market because they are generally new, small companies dealing mostly in research and development in a field largely unknown to insurers. Their inability to obtain coverage causes them difficulty in obtaining bank financing, which, in turn, causes some of these companies to sell out or forego promising research. The industry is exploring the creation of a captive.

Oil and Gas Drilling

The International Association of Drilling Contractors represents 1,500 contractors operating drilling rigs. It estimates maritime liability premium increases of 300% to 700% and inland liability premium increases of 100% to 150%.

Construction Contractors

Constructor magazine (October 1985) estimates average increases in general liability coverage of 40% to 75%. For contractors who were able to negotiate significant discounts in past years increases currently are running up to 300%. In 1985 premium increases for umbrella coverage were approximately 300% for less coverage.

Natural Gas Transportation

The National L-P Gas Association represents 4,100 firms that prepare and transport liquefied petroleum gases for residential and industrial users. According to a spokesman, as many as 25% of the transporters are operating with less than the $5 million in insurance coverage that is required of motor carriers by federal law. Difficulties are attributed to unavailability and prohibitive costs of umbrella insurance.

General Manufacturing

The Machinery & Allied Products Institute ("MAPI") recently conducted a survey of 81 companies producing a broad range of products in the manufacturing industries and obtained an 80% response rate. The typical respondent experienced increases for every type of insurance covered in the survey. The survey covered general liability, D & O, environmental impairment liability, products and other property and casualty coverages. The size of the increases varied with the date of the renewal; consequently, the survey results understate the problem since many of the respondents are not up for renewal until early this year. Significant survey results are shown in the table below.

MAPI Survey Results on Liability Coverages

Premiums	% Higher	% Change (Median)
CGL-Primary	73	40
CGL-Excess	100	250
D & O	72	300
EIL	94	60
Products	95	116
Other	87	40
Lower Limits	**% Lower**	**% Change (Median)**
CGL-Primary	13	-36
CGL-Excess	66	-50
D & O	27	-25
EIL	59	-50
Products	33	-50
Other	18	-25
Deductibles & Exclusions	**% Higher Deductible**	**% More Exclusions**
GCL-Primary	34	97
GCL-Excess	25	96
D & O	49	95
EIL	50	89
Products	50	100
Other	28	100

In addition to the foregoing, 35% of the MAPI respondents indicated that their general liability coverage excluded "sudden and accidental" pollution coverage, while 49% indicated that it was excluded in some layers and included in others. Some 65% of the respondents indicated that they had some coverages cancelled since January 1, 1985.

Machine Tool Manufacturers

The National Machine Tool Association represents 300 to 400 businesses that manufacture heavy machinery which cuts, shapes and forms metal. Preliminary results of a survey indicated product liability premiums have doubled since 1984, and that about half of the respondents have been or expect to be put on claims-made policy forms.

Battery Recycling & Smelting Companies

Battery recycling companies are typical of many industries where processes create toxic wastes. Recycling 50 million scrap batteries accounts for up to 50% of the annual lead smelter production. If the batteries are not recycled, they will be disposed of in landfills, leading to more serious toxic exposure. One major smelting company was offered a $10 million policy with a $2.5 million deductible at a cost of $650,000. While it deems the policy uneconomic, it has not found an alternative. The problem is widespread with smelters of various metals. The uncertainty of the risk and size of pollution liabilities has lead to substantial reductions in coverage with sharp increases in deductibles and premiums.

Power Equipment Manufacturers

Outdoor power equipment manufacturers had been reporting premium increases of from 50% to 70% during the past year. At the end of the year, with many renewals coming due, some have experienced increases of 400% to 600%. The Association once again is considering establishment of a captive.

General Aviation Manufacturers

The General Aviation Manufacturers Association reports that the cost of liability insurance per aircaft was $51 for the 6,778 business, commuter and private aircraft delivered in 1962, and increased to $211 for the 9,774 delivered in 1972. Currently, for the 2,000 planes delivered in 1985, the liability insurance cost has increased to $70,000 per plane. The cost of liability insurance to air frame manufacturers in 1985 was about $135 million, with a total cost of $175 to $200 million for the entire industry that includes manufacturers of engines, electronics and parts.

Ski Operators

Liability insurance premium increases of up to 400% have been reported by the National Ski Areas Association. Some small ski areas have closed, and the average price of lift tickets has increased substantially.

Aerospace Equipment Manufacturers

Aerospace equipment manufacturers are increasingly concerned that the escalating cost of product liability insurance and other associated costs are causing them to lose their ability to compete with overseas manufacturers of similar equipment.

III. THE NATURE AND EXTENT OF THE INSURANCE AVAILABILITY/AFFORDABILITY CRISIS

The above examples of insurance availability, affordability and adequacy problems demonstrate the broad scope of the liability insurance crisis in the mid-1980's. In a similar crisis in the mid-1970's, the problem areas were largely confined to medical malpractice and product liability. Medical malpractice coverage has been a continuing problem, with almost half that coverage currently underwritten by doctors' and hospitals' mutuals and other alternative markets. Product liability coverage, however, was readily available at declining cost during the late 1970's and early 1980's.

A growing capacity shortage over the last year or more has caused commercial insurers to review carefully their underwriting standards and pricing policies in order to determine where insurance capacity can be utilized most profitably. The inevitable result of this reevaluation has been a severe disruption for insurance buyers.

Insurance Availability

Availability problems are occurring in certain specialty commercial insurance markets. These include pollution, day care, municipal, liquor, motor carrier and D & O liability coverages. The bankruptcies of some specialty insurers, particularly in the lines of motor carrier and liquor liability, have affected the capacity in these coverages.

In each of these lines, insurers have perceived the possibility of significant losses based on highly publicized verdicts and settlements. General line insurers who ordinarily would fill the gap left by specialty carriers are unwilling to do so because they can use their scarcer dollars in less volatile and more profitable lines.

Insurance Affordability

Premiums are increasing in virtually all commercial coverages. Examples of affordability problems include nurse-midwives and general aviation manufacturers, both of which face premium costs which may be warranted by the experience, but are too expensive for the buyers. Solutions to problems like these appear to lie outside of the insurance system.

Insurance Adequacy

Problems of insurance adequacy are being experienced across all commercial lines of coverage. The main problem seems to lie with the fact that many buyers are unable to buy as much

insurance as they desire. This is particularly true for large firms which seek large amounts of excess and higher limits coverage. These problems appear related in part to a capacity crunch created both by the insurance cycle and the withdrawal of capacity by the overseas reinsurers. The lack of capacity related to the insurance cycle shows signs of abating as the corner of the cycle has turned and surplus is increasing. But many firms may have to use alternative market mechanisms for at least a couple of years until this capacity fully returns. It may take much longer to get reentry by overseas reinsurers who have grave concerns about the American tort liability system. A second area of inadequacy lies in the growth of exclusions, deductibles and other policy limitations that are just now being introduced into the market. These are discussed in Chapter 3.

The Insurance Availability/Affordability Crisis

Finally, it should be noted that the crisis in insurance availability and affordability does not appear to be a crisis for the insurance industry. While the industry (as discussed in Chapter 2) is suffering substantial underwriting losses, the Working Group does not perceive this crisis to be a major threat to the financial viability of the industry. Rather, it is a crisis for the insureds who cannot obtain or afford the insurance they believe necessary for their on-going activities. And, to the extent that entities are forced to operate without insurance or with inadequate insurance, it is a crisis for victims of tortious conduct who may find that liable defendants cannot pay them their damages.

CHAPTER 2

THE CAUSES OF THE CRISIS IN INSURANCE AVAILABILITY AND AFFORDABILITY

A number of reasons have been proffered for the crisis in the availability, affordability and adequacy of liability insurance. Many of these reasons relate to the economic decisions and performance of the insurance industry over the past decade. Other reasons focus on recent developments in tort law. While the two in fact are closely related, this Chapter discusses each of these areas separately. Part A deals with the general economic reasons for the current crisis; Part B reviews the contribution of tort law. 1/

1/ There have been suggestions that the availability/affordability crisis may be caused by certain aspects of state regulation. While some regulatory measures may have aggravated the problem, the Working Group has found little compelling evidence that the crisis is the result of a regulatory failure, either in the sense of insufficient or inadequate regulation, or in the sense of ill-conceived regulation. In this regard, it is worthwhile noting the 1977 report of the Department of Justice to the Task Group on Antitrust Immunities on The Pricing and Marketing of Insurance, which concluded that "in the commercial lines . . . state regulatory schemes are largely illusory and that insurers are generally free to set their own prices." Id., at vii. The report further indicated that rigid state rate regulation, such as is found in automobile insurance, may in fact aggravate an availability problem. Id., at vi.

In this regard, it is worth noting the conclusion of the Medical Malpractice Policy Guidebook (1985), prepared by Henry Manne (general editor) and Barry Anderson, Patricia Danzon, Clark Havighurst, Charles Phelps and Frank Sloan (principal authors) for the Florida Medical Association. The Guidebook concluded that it was difficult to fault the state insurance regulatory system for the high medical malpractice insurance premiums in Florida. Id., at 11. The report concluded that premium increases lag claims costs, and that "malpractice premiums are almost certainly not 'too high' compared to the increases in claims costs emerging over recent years." Id., at 149-50.

Some have pointed to state insurance reserve requirements as a cause of the insurance availability/affordability crisis, to the extent that they believe these requirements to have exacerbated capacity constraints. While the Working Group did not analyze whether state reserve requirements are too high or too low, it should be noted that these requirements exist to ensure the solvency of insurance carriers, and thereby to protect insureds. It also should be noted that the only way that state insurance reserve requirements conceivably could be modified to

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A.

I. INSURANCE INDUSTRY PERFORMANCE

Recent news accounts have presented a seemingly conflicting view of the economic performance of the property-casualty insurance industry. In order to understand the financial condition of the industry itself and of some of its specific lines of business, it is useful to compare the condition of the industry as a whole to what has been happening to premiums in the lines which present significant availability/affordability problems.

The table below presents premium and loss data for the property-casualty insurance industry for the period 1981 through 1985.

Year	Net Premiums Written (000)	Loss and LAE (000)	Expenses (000)	Statutory Underwriting Loss after Policyholder Dividends (000)
1981	$ 98,805,725	$75,764,229	$27,132,052	$- 6,323,534
1982	103,115,653	82.152,241	28,996,122	-10,415,751
1983	107,802,698	87,719,055	30,799,231	-13,285,049
1984	117,743,957	103,720,652	32,980,082	-21,455,300
1985*	142,300,000	126,846,220	37,353,750	-25,200,000

*Estimated

Source: Best's Insurance Management Reports

The most striking number in the table, of course, is the $25 billion underwriting loss estimated for 1985. This number represents the difference between premiums written and expenses, policyholder

1/ (FOOTNOTE CONTINUED)

produce lower premiums would be if the reserve requirements were relaxed. It would be difficult to justify relaxing reserve requirements, however, in light of the fact that both insurance company insolvencies and the number of insurance companies reported to be in financial difficulty have increased substantially in the last two years.

The Working Group is continuing to review the contribution, if any, of state regulation to the insurance availability/affordability crisis.

dividends, 2/ estimated losses and loss adjustment expenses ("LAE").

The underwriting loss, however, while significant, represents only part of the industry's overall financial picture. Since premiums are collected well in advance of any anticipated payout, they are invested and earn income. In addition, other income is generated which also must be considered in reviewing the industry's financial condition. Overall income in 1985 resulted in the industry showing a $7.6 billion gain in policyholders' surplus (the equivalent of net worth), 3/ on an underwriting loss of $25.2 billion and net investment and other income of $32.8 billion. Thus, the industry appears to have made an overall profit in 1985, though at a lower rate than historical levels or other sectors of the economy.

In discussing the overall financial review of the property/casualty industry, Best's reported that:

> Investor interest in the property-casualty industry cannot be denied. While the Dow Industrial Average had made headlines by surpassing the 1500 mark (a 25% gain for the year), Best's Index of property/casualty companies has jumped 50% at this writing, and security analysts specializing in insurance--and cognizant of 1985's underwriting losses--nevertheless continue to be optimistic about the industry's prospects. 4/

Two factors must be taken into account in assessing the role of the insurance industry's financial performance in the insurance availability/affordability crisis. First, even though the industry currently is making a profit, that profit is well below the profitability of most other major industries, as well as the insurance industry's historical average. For example, in 1984 the property-casualty insurance industry produced an annual rate

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2/ Questions have been raised as to whether or not the $2.1 billion paid out in policyholder dividends should be included in the underwriting loss. Policyholder dividends are offered to some policyholders in some lines, and reduce the net cost of their insurance coverage. Consequently, any reduction in such premiums simply increases the net cost to policyholders.

3/ Policyholders' surplus is the difference between insurers' assets and liabilities. It is considered "the financial security that stands behind every insurance policy and is that which provides the cushion to support the shock of major catastrophe, stock market declines and loss of reserve inadequacies." ISO, Financial Condition of the Insurance Industry -- An Update (1985).

4/ Best's Insurance Management Reports (December 30, 1985).

of return on net income after taxes as a percent of net worth of 1.8%, whereas the median for Fortune 500 companies was 13.6%. 5/ The comparable rate of return for the property-casualty insurance industry from 1975 to 1984 was 10.9%. 6/

Second, the insurance availability/affordability crisis has not manifested itself across the entire spectrum of insurance services, but only in specific lines. These lines account for a relatively small portion of the industry. For example, the entire property-casualty insurance market accounts for only approximately one-third of the overall insurance market in terms of written premiums. 7/ The two property-casualty lines that have been the primary source of availability/affordability problems -- general commercial liability and medical malpractice -- amounted to only 7% of all the property-casualty lines in terms of 1984 written premiums. 8/ (These two lines thus represent approximately 2.5% of the entire industry's written premiums in 1984.) But, as can be seen in Subsection II, about one-fifth of the property-casualty industry's $21.5 billion 1984 underwriting loss came from these two lines. And in 1985, the two lines accounted for almost one-quarter of the property-casualty industry's estimated $25.2 billion underwriting loss. These two lines, as well as the Commercial Multiple Peril line, 9/ are discussed in greater detail in Subsection II.

II. UNDERWRITING RESULTS BY MAJOR LINES

While the industry overall has been profitable, certain lines have made major contributions to the underwriting losses. This section examines the major commercial lines in which availability and affordability problems have been most prominent.

Commercial Multiple Peril

Commercial Multiple Peril ("CMP") is related to the general liability line of insurance in that it is a packaged line of business which includes some commercial general liability coverage and its long-tail losses; that is, losses which may be

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5/ Insurance Information Institute, 1985-86 Property/Casualty Factbook, page 22.

6/ Id. The comparable statutory accounting rate of return was 11.9%. Id.

7/ Congressional Quarterly Weekly Report, page 150 (January 25, 1986).

8/ Insurance Information Institute, 1985-86 Property/Casualty Factbook, page 16.

9/ If the Commercial Multiple Peril line is taken into account, approximately 14% of the property-casualty industry (in terms of 1984 written premiums) accounted for about one-third of its underwriting losses in both 1984 and 1985. Id.

reported many years after the policy year. CMP experience over the past five years is reflected in the chart below.

Commercial Multiple Peril

Year	Net Premiums Written (Billions)	Loss and LAE (Billions)	Underwriting Expenses (Billions)	Statutory Underwriting Loss After Policyholder Dividends (Billions)
1981	$6.8	$4.6	$2.5	$-0.5
1982	6.9	5.3	2.7	-1.2
1983	7.2	5.9	2.9	-1.7
1984	8.2	7.9	3.2	-2.9
1985*	11.7	10.4	4.1	-3.0

*Estimated Source: Best's Insurance Management Reports 12/30/85

While the underwriting losses for CMP rose to $3 billion in 1985, it is readily apparent that until recently there had been little premium growth in the line. Best's predicts that the short-tail, non-liability portion of CMP should provide the ability for a fast turnaround for this line. It also notes that ISO's new CGL claims-made form will be added to the standard CMP form, but that market pressures should assure the availability and affordability of the smaller businessowner's package. 10/

Commercial General Liability

Commercial General Liability ("CGL") coverage includes most of the commercial sectors which are experiencing serious availability/affordability problems. It covers product liability, municipalities, day care centers and other commercial coverages. It is the line for which ISO has introduced its new claims-made form. The experience of this line over the past five years is summarized below.

General Liability

Year	Net Premiums Written (Billions)	Loss and LAE (Billions)	Underwriting Expenses (Billions)	Statutory Underwriting Loss After Policyholder Dividends (Billions)
1981	$6.0	$5.1	$1.8	$-1.0
1982	5.6	5.4	1.8	-1.7
1983	5.7	6.0	1.8	-2.1
1984	6.5	7.8	1.9	-3.2
1985*	11.1	13.2	2.7	-4.6

*Estimated Source: Best's Insurance Management Report

10 Best's Insurance Management Reports (December 30, 1985).

As is apparent, written premiums dropped in 1982 and 1983 and rose slightly in 1984. The figures for 1985, however, show a dramatic increase of 72% over the 1984 premium. Increases are continuing to occur in the line as policies come up for renewal. Losses increased throughout the period, but did so at a relatively even pace until 1984, when losses increased by over $1 billion dollars over the previous year's losses.

Medical Malpractice

Medical malpractice represents only about 1.8% of property/casualty insurance written, but has been the source of major availability/affordability problems. The following chart summarizes the experience of the line over the past five years.

Medical Malpractice

Year	Net Premiums Written (Billions)	Loss and LAE (Billions)	Underwriting Expenses (Billions)	Statutory Underwriting Loss After Policyholder Dividends (Billions)
1981	$1.3	$1.6	$0.2	$-0.5
1982	1.5	2.0	0.2	-0.7
1983	1.6	2.1	0.2	-0.8
1984	1.8	2.8	0.3	-1.1
1985*	2.6	3.6	0.3	-1.4

*Estimated

Source: Best's Insurance Management Report

Medical malpractice experience is receiving considerable attention at the state level. Unlike many lines of coverage such as product liability, rates are based on state claims rather than national data.

III. PREMIUM TRENDS

The recent rapid growth in premiums has been a major element in the current availability/affordability crisis. This section examines this trend. The following data was provided by the ISO.

Cash-flow underwriting is generally acknowledged to have played a role in causing the large underwriting losses presently being experienced in the commercial lines. According to ISO, the industry's current underwriting losses are a result of "a

prolonged period of underpricing and rapidly expanding tort liabilities." 11/ In this regard, the ISO report states:

> For the better part of seven years, the insurance industry has been engaged in a brutal price war. During the early 1980's, the price for commercial insurance was decreasing, sometimes sharply, as insurers vied for premium dollars to invest at the high interest rates then in effect. At the time, commercial customers did not complain. Indeed, many realized that commercial insurance in the United States was being sold below cost, even when investment income was considered. 12/

Chart A, based on ISO data, tracks commercial line premiums in constant 1967 dollars. As can be noted from the chart, 1984 marked the first real increase in premiums (in constant dollars) after five consecutive years of declining written premiums. But 1984 written premiums were almost 20% less than premiums collected in 1978, the year preceding the dramatic decline in premiums. At the same time, losses and expenses in 1984 were at an all-time high. 13/

A similar comparison of the general liability premiums written, premiums earned and line outgo over the past ten years (not in constant dollars) is shown in Chart B.

Analyzing this data, the Best's report notes that during the relevant period (1975 - 1985):

> . . . the inflation of liability awards could have been no secret to any underwriter. Had the ascending line of premiums written that was established in 1975 through 1978 continued to rise, the general liability losses of $13 billion incurred in the last six years largely would have been avoided. 14/

11/ ISO, Financial Condition of the Insurance Industry -- An Update (1985).

12/ Id.

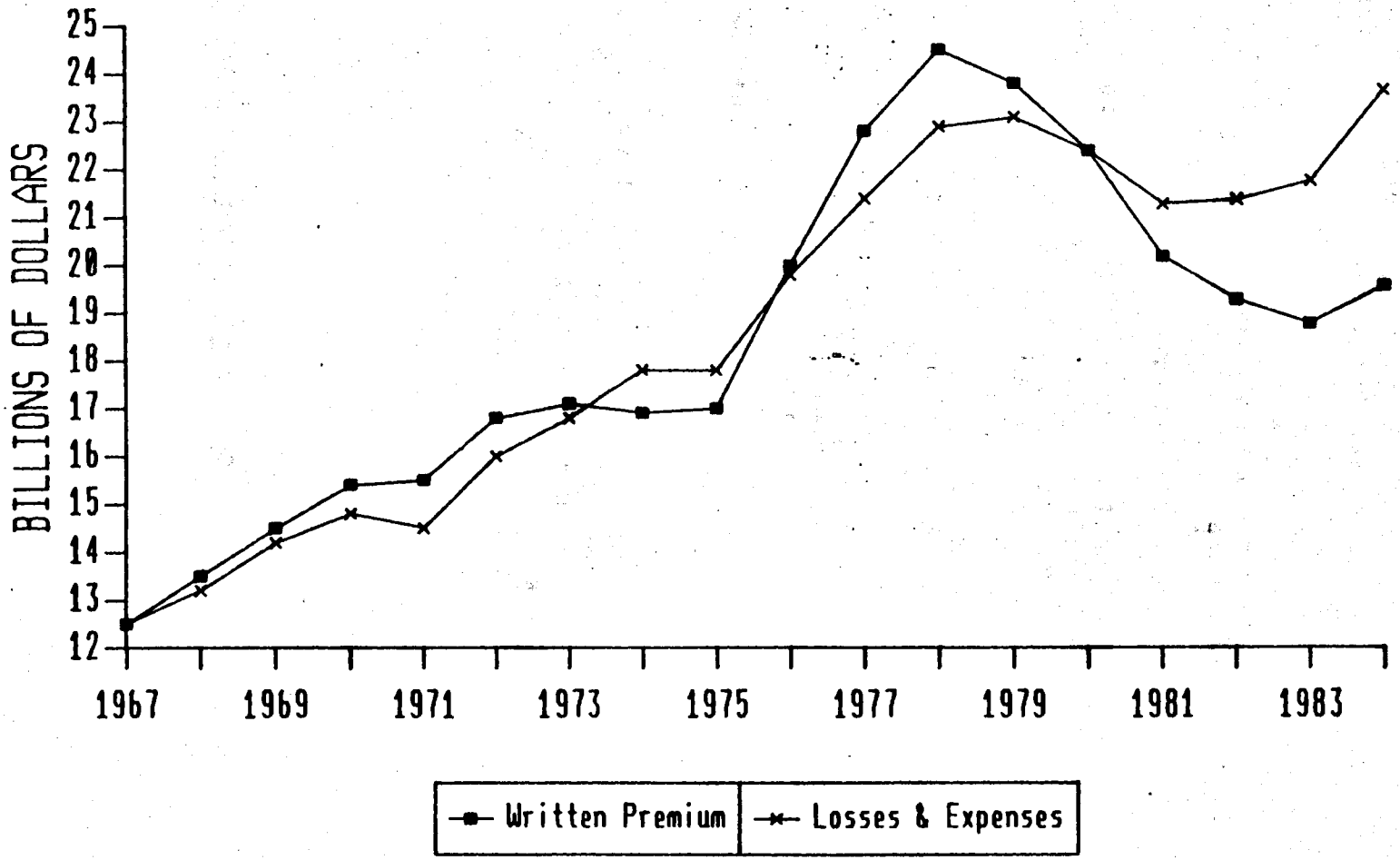
13/ Id.

14/ Best's Insurance Management Reports (December 30, 1985).

CHART A

WRITTEN PREMIUM vs. LOSSES & EXPENSES

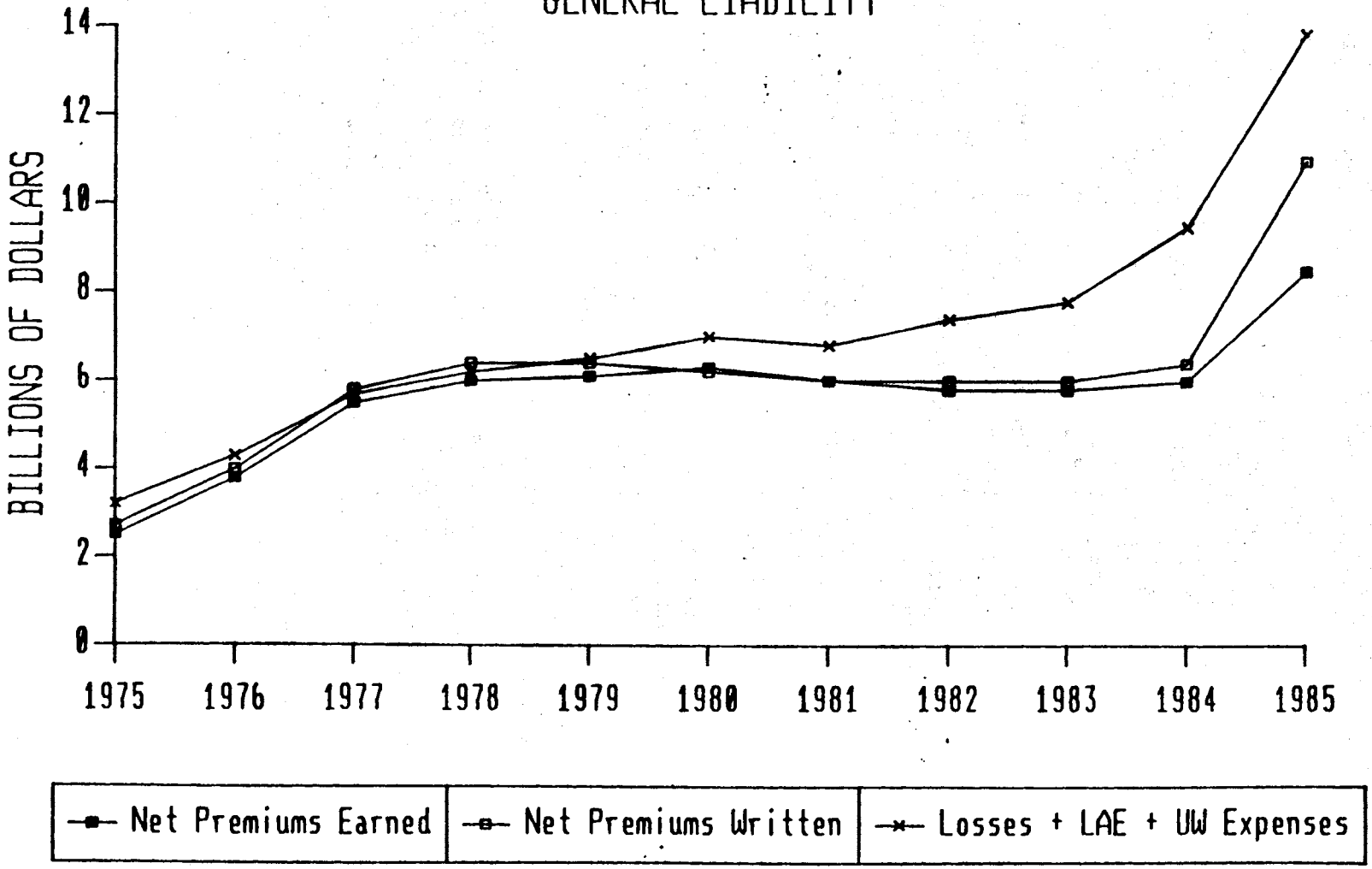
COMMERCIAL LINES IN CONSTANT 1967 DOLLARS



Source: Insurance Services Office

CHART B

GENERAL LIABILITY



Source: Best's Insurance Management Report, 12/30/85

IV. THE ECONOMIC CAUSES OF THE INSURANCE AVAILABILITY/AFFORDABILITY CRISIS

The above discussion indicates that during the late 1970's and early 1980's the insurance industry engaged in significant premium reductions while claim losses increased steadily. The result, not surprisingly, has been massive underwriting losses in recent years.

It is useful in considering the contribution of such economic factors to the insurance availability/affordability crisis to distinguish two different effects which frequently are confused. The first is the inflationary effect on premiums of the recent decline in interest rates. The second is the premium cutting which took place in the late 1970's and early 1980's as a consequence of the industry's desire to take advantage of high interest rates available during that period.

As to the first effect, there is an obvious inverse relationship between premiums and the prevailing interest rate. A significant portion of an insurer's profits stem from the return on the premium income it invests between receipt of the premium and payout of the incurred liabilities. When interest rates are high, premiums tend to be lower since more of the insurer's income comes from such return on investment; and when interest rates are low, premiums will tend to be higher since the insurer is more dependent on the premium principal to cover the anticipated payout. Thus, as interest rates fall -- as they have in the mid-1980's -- insurance premiums inevitably increase.

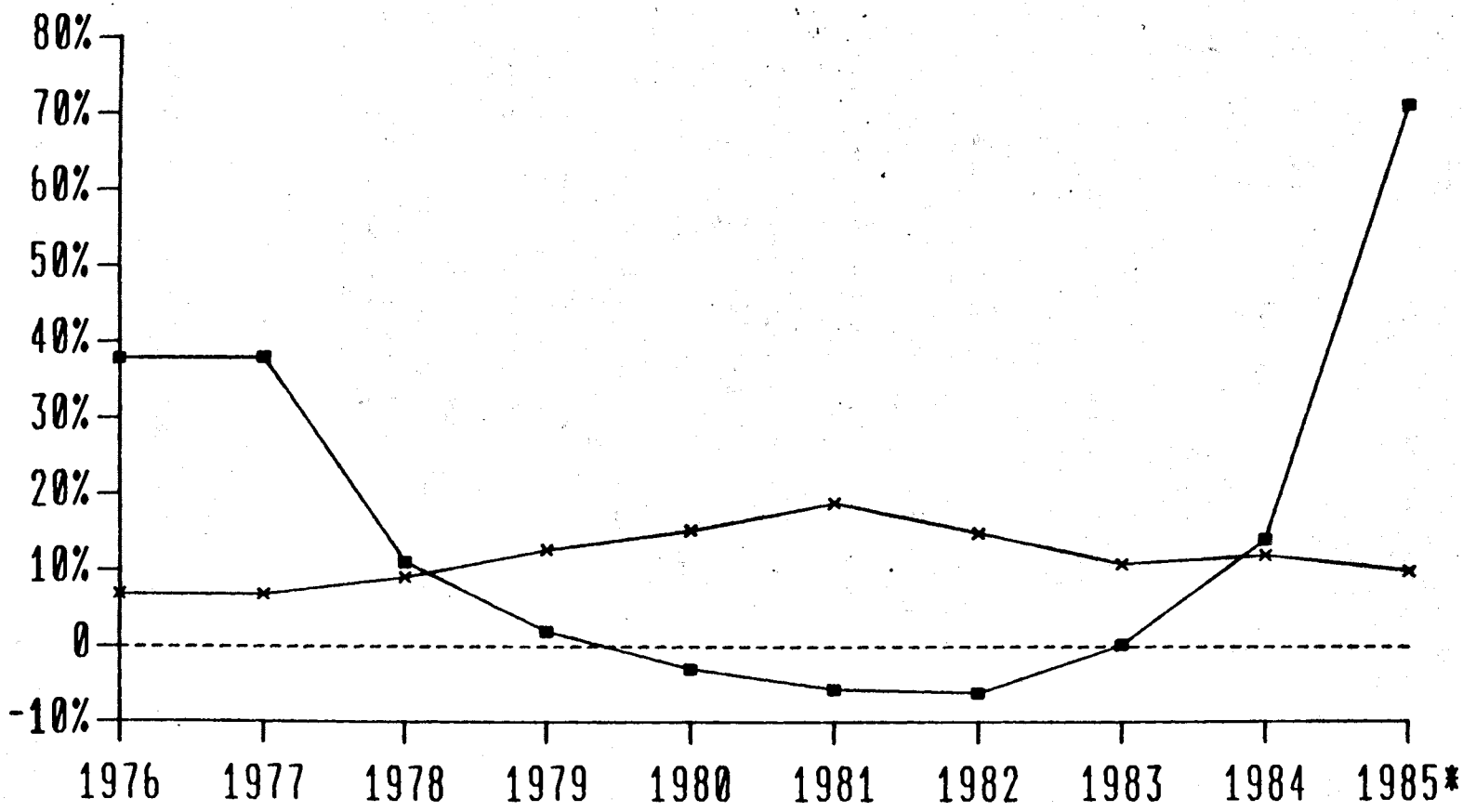
This inverse relationship is illustrated by Chart C, which compares the prime rate in 1976 through 1985 to the annual percentage change of the total Commercial General Liability (CGL) premiums written by the insurance industry in each of those years. 15/ Chart C graphically demonstrates that the rate of growth of the written premiums changes inversely with the movement of the prime interest rate.

To the extent that the recent sharp premium increases are related to the drop in interest rates, there is little the federal (or any) government can or should do to mitigate this market effect. Declining interest rates cause innumerable economic realignments which, on the whole, are quite beneficial to the economy. An increase in insurance premiums resulting from such a reduction in interest rates, while of itself undesirable, is a relatively minor side effect to the far more significant economic consequences of a drop in the interest rate.

15/ The percentage change in 1976 through 1984 is obtained from the Insurance Information Institute's most recent Property/Casualty Factbook. The estimate for 1985 is obtained from the ISO data discussed supra.

CHART C

PERCENTAGE CHANGE IN GCL PREMIUMS COMPARED TO INTEREST RATE



*1985 Data Estimated

Moreover, there is little that can be done to address this source of premium volatility. It would be absurd to try to keep interest rates high simply to keep insurance premiums as low as possible. But as long as interest rates fluctuate, premiums necessarily will reflect such changes.

A second economic factor related to interest rates is the extent to which high interest rates may have triggered "excessive competition" in the insurance industry which led the industry to sell its product too cheaply. For one thing, even assuming one accepts the concept of "excessive competition," it is unclear how such losses in fact contribute to the insurance availability/affordability crisis. As discussed later in this Chapter, such losses are "sunk costs" which the industry cannot recoup simply by charging higher premiums. If premiums in fact are higher than the insured risks and the currently available investment return dictate, either other sources of capital (including insurers who have suffered no losses or lower losses) should offer the same insurance at a lower price, or insureds will retain these "excess profits" for themselves through self-insurance or the formation of captives. The fact that there appears to be little insurance coverage being made available by new or expanding underwriters, and that many insureds are highly reluctant to self insure or form captives (even though many with serious availability problems may have no alternative), strongly indicates that recoupment of losses is not a particularly compelling explanation for the current insurance availability/affordability crisis.

It is particularly puzzling that the proponents of this theory advocate the abolition of the insurance industry's antitrust immunity contained in the McCarran-Ferguson Act (Public Law 79-15) as an appropriate response to the asserted problem of the industry's cash-flow "mismanagement." It is hard to reconcile the argument that the current problems of the insurance industry stem from "excessive competition" with the proffered solution of removing the industry's antitrust immunity. Since the goal of antitrust law is to enhance competition, if one truly believes that the problems of the insurance industry are a result of too much competition, the last thing one would advocate is a legal change which would increase the level of competition. While the Working Group did not review and takes no position on the continuing validity of the industry's antitrust immunity, 16/ it is readily obvious that the suggestion that allegedly "excessive competition" can be cured by even more competition is patently absurd.

16/ Despite the assertions of some, the Working Group found no evidence to suggest that the industry's antitrust immunity is a significant factor in the insurance availability/affordability crisis. It should be noted, however, that the immunity has been criticized for a variety of other reasons. See the 1977 report of the Task Force on Antitrust Immunities, footnote 1, supra.

The reasons why the loss recoupment (or excessive pricing) theories advocated by some make little economic sense can briefly be summarized as follows:

- Insurers, like all profit maximizing companies, charge the price which maximizes their profits. Past gains or past losses are irrelevant to setting the price today which will maximize profits tomorrow. The argument that insurers are charging higher premiums to recoup past losses suggests that absent such losses their premiums would be lower -- that is, that they would not be charging premiums that maximize their profits. That makes little sense.

- Even if excessive premiums were being charged by some insurers to recoup their past losses, for the reasons discussed, other insurers would offer the same coverage at lower prices reflecting the actual risk, or insureds would retain such excess profits for themselves through self-insurance or the formation of captives. 17/

- The commercial lines of insurance, which are at the center of the availability/affordability crisis, in fact are relatively competitive. For example, the 1977 report of the Task Force on Antitrust Immunities (see footnote 1, supra) found that the property-liability insurance industry "appears to possess an atomistic market structure," including over 900 companies. Id., at 7. 18/ The Task Force also found that the restrictions to entry do not appear significant in the property-liability insurance industry, id., at 9, and that there appears to be price competition in this line as a result of "an industry structure that favors competition." Id., at 27-28. 19/ It is, of course,

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17/ Many insurance companies are mutuals, meaning that they are owned by their policyholders. The suggestion that they are charging their policyholder-owners unnecessarily high premiums makes even less sense, since any such excess profits must be rebated through policyholder dividends.

18/ The report states that 20 insurance groups account for 53% of written premiums, and that no single group accounts for a major share of the market. Id., at 8. This is consistent with the analysis of the Medical Malpractice Policy Guidebook (H. Manne, 1985), which found the medical malpractice insurance market in Florida to be "substantially and effectively competitive." Id., at 166.

19/ See also page 348 of the report summarizing the Task Force's

(CONTINUED)

difficult to conceive how premiums are being kept at artificially high levels for a line of insurance in which prices appear to be competitively determined.

- Finally, many of the strongest proponents of the loss recoupment theory also contend that these losses were the result of excessive price competition in the industry. Obviously, it is difficult to reconcile these arguments. 20/

In sum, to the extent that purely economic factors underlie the insurance availability/ affordability crisis, they do not appear to be the type of problems which can be cured by different or more intensive forms of government regulation -- either at the state or federal level -- of the insurance industry. There, however, is a cause of the availability/ affordability crisis at the very heart of that crisis which the government is well placed to address in a variety of constructive ways. That cause is tort law, and its role in the crisis is discussed in Part B of this Chapter.

B.

The above discussion has focused largely on the current financial condition of the insurance industry, and the economic factors leading to that condition. The following discussion examines the state of tort law, and its central role in the insurance availability/affordability crisis.

Unlike the above related economic data on the insurance industry, it is difficult to obtain good empirical data indicating precisely what has happened to tort liability in

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19/ (FOOTNOTE CONTINUED)

conclusion that the "industry is structured in a manner conducive to competition." It should be noted that these conclusions did not appear to apply to some other lines of insurance such as life insurance.

20/ These same points apply equally well to arguments that premiums are set excessively high to recoup losses resulting from mismanaged investment portfolios. Just as past losses are irrelevant to determining the premiums which will maximize profits, investment portfolio losses should have no bearing on premiums. In this regard, however, it should be noted that the property-casualty industry made $32.8 billion from net investment and other income in 1985. See supra.

recent years. 21/ It is plain even to the most uninitiated that tort law has changed dramatically in recent years -- from a relatively quiescent legal backwater into one of the most important and dynamic areas of the law today. 22/ Moreover, a growing body of case examples and empirical data suggest that the current tort system has serious problems and is operating quite poorly. The insurance availability/affordability crisis is one symptom -- albeit the most dramatic and acute symptom -- of the dislocations and problems generated by a malfunctioning tort system.

I. PROBLEM AREAS IN TORT LAW

In attempting to understand what has happened to tort liability in the United States, the Working Group has focused on four interrelated areas: fault, causation, damages and transaction costs. Each is discussed separately below.

The Movement Toward No-Fault Liability

One of the most disturbing aspects of the current tort system is the degree to which it has moved toward no-fault liability. While this movement began in earnest over twenty years ago, it appears to have accelerated dramatically in recent years.

Beginning in the early to mid-1960's it became fashionable to reject the twin pillars upon which tort law historically had been constructed -- deterrence and compensation -- in favor of seemingly more enlightened theories based largely on concepts of societal insurance and risk spreading. 23/ While many of these

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21/ The Rand Corporation, through its Institute for Civil Justice, has produced the best empirical data and analyses available in the area. While the Institute has only been able to research discrete areas of civil justice, the conclusions drawn from those analyses are invaluable to understanding many broader problems. The recently published five-year overview of the Institute's program offers an excellent summary of the research, results and continuing work of the Institute's staff.

22/ For example, at the end of fiscal year 1975, what is now the Torts Branch of the United States Department of Justice contained 39 attorneys, who handled or supervised about 4,000 cases totalling approximately $1 billion in claims. At the end of fiscal year 1985, the Torts Branch had grown to 124 attorneys handling or supervising about 11,000 cases totalling approximately $200 billion in claims.

23/ One of the most explicit statements of such a theory can be found in the decision of the New Jersey Supreme Court in Beshada v. Johns-Manville Products Corp., 90 N.J. 191, 447 A.2d 539 (1982), in which the Court expressly denied defendants

(CONTINUED)

theories were couched in terms of economic efficiency, they represented the beginning of a devastating, and to this day, on-going challenge to the role of fault as a predicate of tort liability. The long-term effect of this development has been less to promote a more efficient or sensible tort system, 24/ than to undermine the importance of fault (or wrongdoing) as a moral and doctrinal justification for and limitation on tort liability. As this limitation has been removed or undermined in certain areas of tort liability, tort law increasingly has come to rest only on the pillar of compensation, with compensation often awarded merely for the sake of compensation.

As the tort system moves away from fault it increasingly imposes liability upon persons and companies that have done nothing wrong. This has been accomplished in a variety of ways: by directly reducing or even eliminating the fault requirement; by

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23/ (FOOTNOTE CONTINUED)

the opportunity to raise a "state of the art" defense. The Court held that even if the danger at issue was scientifically unknowable at the relevant time, defendants nonetheless were still liable for having failed to warn of an unknowable risk. As justification for its holding, the Court relied heavily on risk spreading. In the words of the Court, "manufacturers and distributors . . . can insure against liability and incorporate the cost of the insurance in the price of the product." 447 A.2d at 547. The Court went on to opine that the likely increase in premiums to compensate for unanticipated risks was "not a bad result." Id.

24/ The belief that tort liability should be no-fault so as to serve as a risk spreading mechanism for all injuries is in fact quite anti-consumer. Such a view of tort liability effectively would mean that the price of every product and service would include an insurance surcharge for the risk of any injury related to the product or service. It has long been understood, however, that because of the extraordinarily high transaction costs of the tort system, such compulsory insurance through the tort system would be among the most inefficient and costly ways for consumers to purchase insurance. Thus, for every $1 of compensation, the tort system requires the consumer to pay approximately $3 in premiums (assuming, as discussed infra, two-thirds transaction costs), while that same $1 of compensation can be obtained through first-party health and disability insurance for only $1.25. H. Manne, Medical Malpractice Policy Guidebook 143 (1985). It is highly ironic that many proponents of no-fault liability argue that such liability is in the best interest of consumers. In fact, since consumers ultimately pay the premiums of whatever compensation scheme is devised, quite the contrary is the case. See also Epstein, "Products Liability as an Insurance Market," 14 J. Legal Stud. 645 (1985).

defining new duties that effectively create fault where no fault existed previously; and, by engaging in after-the-fact analyses that "find" fault wherever there has been an injury. 25/ The ultimate effect of these developments has been the same -- to shift liability for compensation to "deep pocket" defendants that have the resources to compensate plaintiffs generously. 26/

Fault has not, however, been openly (or completely) rejected as part of our tort law. One reason is that fault remains the only vehicle in tort law capable of distinguishing wrongful (or undesirable) from beneficial (or desirable) conduct. If fault were rejected altogether, it would mean that desirable activities would be just as likely to incur liability as wrongful conduct. An open rejection of fault thus necessarily would result in a sweeping transformation in the public's attitude toward tort law, which continues to be bottomed on the concept of tort liability as a form of justified redress for wrongful conduct. A second reason why fault continues to be part of tort law (and why courts often will engage in amazing distortions of relevant facts or legal doctrines to find fault rather than simply reject the principle of fault) is that fault is the basis of much of the structure and process of tort law.

25/ The duty to warn has been a particularly fertile ground for such after-the-fact compensation oriented findings of fault. It is all too easy after the occurrence of an injury to postulate a warning that might have influenced the plaintiff to be more careful or to reconsider his action, no matter how fanciful or unreasonable such a warning might appear prior to the injury. Such analyses have been a major factor in the medical malpractice and product liability litigation explosion.

26/ A recent and almost classic example of such compensation oriented liability findings is the California Supreme Court's decision in Bigbee v. Pacific Tel. & Tel. Co., 34 Cal.3d 49, 665 P.2d 947 (1983). In that case, a man was injured when an allegedly intoxicated driver lost control of her car, veered off the street into a parking lot, and crashed into a telephone booth in which the man was standing. Suit was brought against the companies responsible for the design, location, installation, and maintenance of the booth. The Court, in an opinion authored by Chief Justice Rose Bird, found that the risk that someone might veer off the road and crash into the phone booth was not unforeseeable as a matter of law. The Court also determined that it was of no consequence that the harm to plaintiff came about through the negligent or reckless acts of an allegedly intoxicated driver. In a concluding footnote, Chief Justice Bird stated that "there are no policy considerations which weigh against imposition of liability" against the defendants even though their "conduct may have been without 'moral blame,'" and referred specifically to "the probable availability of insurance for these types of accidents . . . ." 665 P.2d at 953 n. 14.

If fault were no longer a central element in determining liability, the current tort system would in many ways be wasteful, inefficient and unfair in the extreme. 27/

Tort law thus has gradually (with a marked acceleration in recent years) been moving in the direction of no-fault liability without an adequate acknowledgement of either the existence or the implications of this development. The result is an increasingly common and perverse combination of fault-based levels of compensation based on no-fault liability.

The Undermining of Causation

Tort law traditionally has sought to place liability only upon those actors whose wrongful conduct actually caused an injury. This principle is found in the concept of "proximate cause," which requires a reasonable relationship between a given cause and effect. For some time, however, proximate cause has been under systematic attack. No single doctrinal change can be identified as the primary vehicle for this attack. Rather, the challenge has come through a variety of questionable practices and doctrinal innovations.

One such development has been the increasing use of joint and several liability to shift the cost of compensation to "deep pockets." Joint and several liability developed in the context of defendants acting in concert. 28/ Over the years, however, it increasingly has been used to make a defendant with only a limited role in causing an injury bear the full cost of compensating plaintiff, even in some cases where the plaintiff may have been largely responsible for his own injury. 29/ The result has been that joint and several liability in the absence of concerted action can and does lead to highly inequitable

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27/ For example, the way in which damages are measured and awarded can only be justified, if at all, on the basis of redressing wrongful conduct. Once wrongdoing is removed as an element of liability, many of the principles involving damages become grossly unfair.

28/ See generally Prosser and Keeton on Torts (5th ed. 1984), Chapter 8. As may be obvious, as with so many other aspects of tort law, fault remains a central and essential justification for joint and several liability.

29/ The application of joint and several liability in cases where there in fact is no concerted action is discussed in some detail in Speiser, Krause & Gans, The American Law of Torts § 3:7 (1983). It is interesting to note that the English courts apparently have maintained the traditional common law basis for joint and several liability, and have refused to apply such liability in the absence of concerted action. Id.

treatment of defendants, particularly "deep pocket" defendants. 30/

A related development is the way in which joint and several liability has been applied by some courts to theories of "enterprise" or "market share" liability for injuries caused by generic products (e.g., DES). "Market share" liability, in its pure theoretical sense, allocates liability among manufacturers of a generic product on the basis of their share of the relevant market. While there can be some serious problems and inequities with this approach, as long as all relevant manufacturers (and their respective market shares) are accounted for, and the product is truly generic in nature, such an allocation of liability may be the only way plaintiffs in some cases can obtain compensation for injuries caused by wrongdoing on the part of the manufacturers of such a product. Serious problems with this approach arise, however, when not all relevant manufacturers are accounted for, or where the product is not truly generic in nature. Even more troublesome is the approach of several courts which use some industry liability allocation formula, but then apply joint and several liability to all defendants. See, e.g., Abel v. Eli Lilly & Co., 418 Mich. 311, 343 N.W.2d 164, cert. denied., 105 S.Ct. 123 (1984); Collins v. Eli Lilly Co., 116 Wis.2d 166, 342 N.W.2d 37 (1984). This, in fact, represents a clear abuse of joint and several liability, and cannot be justified on the basis of the unique difficulties plaintiffs sometimes face in identifying the manufacturer of an injury causing generic product.

A third means that has been used to undermine causation -- increasingly common in toxic torts cases -- is the use of presumptions or burden-shifting techniques to force the defendant to prove the lack of causation in order to avoid liability. 31/ Frequently, this amounts to asking the defendant

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30/ The legal doctrine of contribution in theory could serve to mitigate some of those inequities. In certain areas of the law, such as antitrust law, where joint and several liability generally tends to be applied to established businesses, contribution appears to function quite well. (And, in any event, joint and several liability in antitrust cases is virtually always based on concerted action -- the traditional basis for such liability.) In personal injury cases, however, many multi-defendant cases involve a "deep pocket" and one or more defendants who are either judgment proof or have limited assets or insurance coverage. In such cases, the belief that contribution serves as a mitigating factor is largely illusory.

31/ A particularly dramatic example of such a practice can be found in Allen v. United States, 588 F.Supp. 247 (D. Utah 1984), a low-level radiation exposure case in which the court shifted to the government the burden of proving that particular cancers were not caused by radiation exposure.

to meet an impossible burden of proving the negative.

Another way in which causation often is undermined -- also an increasingly serious problem in toxic tort cases -- is the reliance by judges and juries on noncredible scientific or medical testimony, studies or opinions. It has become all too common for "experts" or "studies" on the fringes of or even well beyond the outer parameters of mainstream scientific or medical views to be presented to juries as valid evidence from which conclusions may be drawn. The use of such invalid scientific evidence (commonly referred to as "junk science") has resulted in findings of causation which simply cannot be justified or understood from the standpoint of the current state of credible scientific and medical knowledge. 32/ Most importantly, this development has led to a deep and growing cynicism about the ability of tort law to deal with difficult scientific and medical concepts in a principled and rational way.

These are but four developing areas that are causing defendants to be found liable for injuries they did not cause. The one common attribute of these developments is that the defendants to whom liability is shifted almost invariably happen to be those with the deepest pockets.

The Explosive Growth in Damage Awards

Another area of great concern is the explosive growth in tort damages awards over the last decade. A few statistics will illustrate this point.

Jury Verdict Research, Inc., publishes data on the average jury verdict in product liability and medical malpractice cases. The service's latest report 33/ shows that the average medical

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32/ An instructive decision in this regard is the district court opinion in Johnston v. United States, 597 F.Supp. 374 (D. Kansas 1984). The court there exhaustively reviewed the theories and credentials of a number of plaintiffs' experts on the effects of low-level radiation, and rejected their testimony as biased, contradictory and totally without scientific merit. Of particular interest is the court's frustration that these same experts had played prominent roles in major radiation cases such as Silkwood and Allen, and that their testimony was being used in numerous cases throughout the country. The court noted its disappointment that such "so-called experts can take such license from the witness stand [to] say and conclude things which . . . they would not dare report in a peer-reviewed format." Id. at 415.

33/ Jury Verdict Research, Inc., Injury Valuation: Current Award Trends No. 304 (1986). The 1985 data provided by the service is incomplete, and is subject to refinement. The (CONTINUED)

malpractice jury verdict increased from $220,018 in 1975 to $1,017,716 in 1985 (see Chart D), a 363% increase. 34/ Average product liability jury verdicts during this same period increased from $393,580 to $1,850,452, a 370% increase (see Chart E). 35/

Interestingly, much of this increase can be attributed to a remarkable growth in verdicts above $1 million. In 1975 there were three million-dollar medical malpractice verdicts and nine million-dollar product liability verdicts reported by Jury Verdict Research, Inc. In 1984, the numbers had grown to 71

33/ (FOOTNOTE CONTINUED)

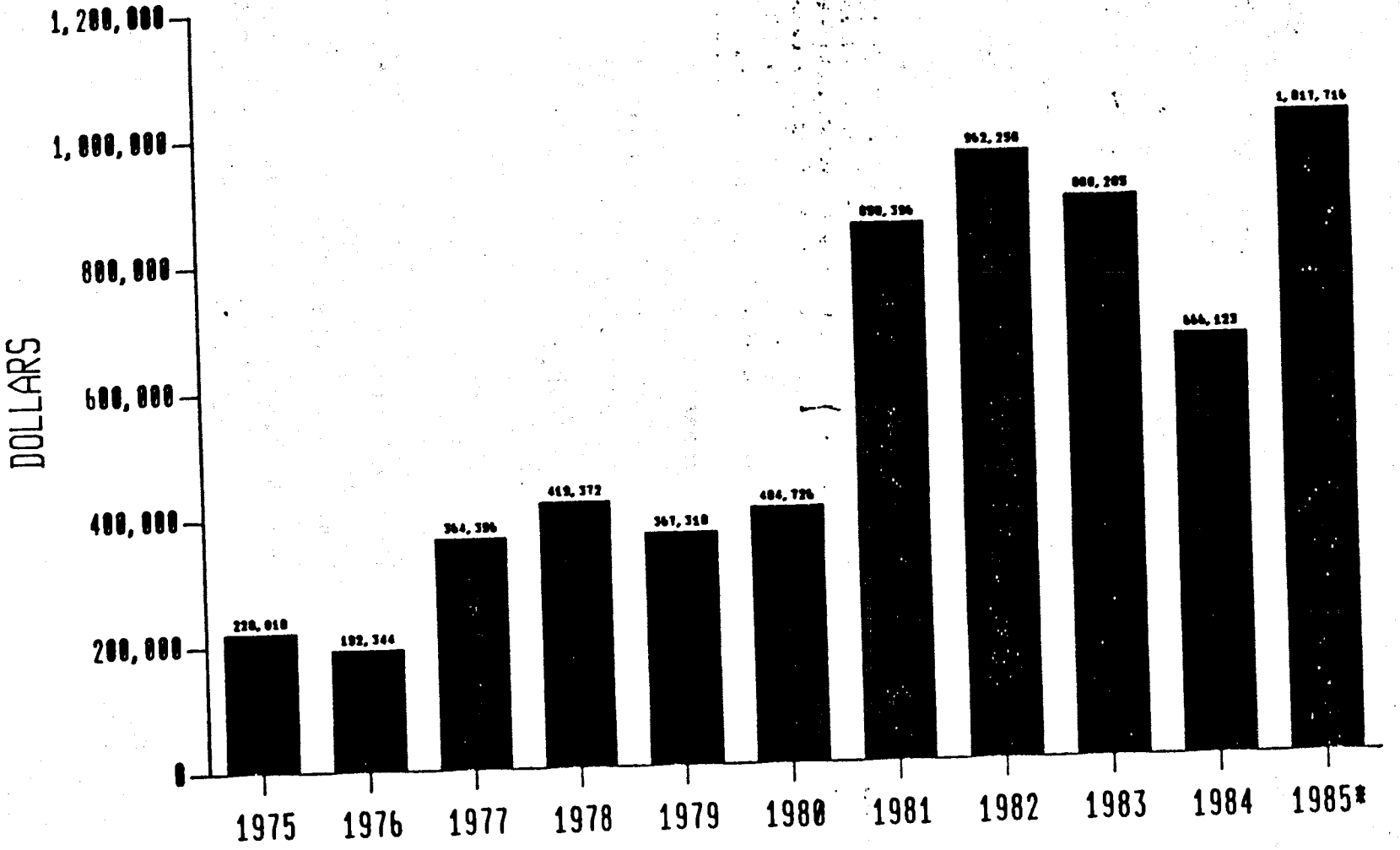
service indicates that it bases "its findings, values and probabilities upon collected verdicts using accepted statistical methods in their analysis and application." Nevertheless, the reported average annual verdicts are not used by the Working Group as an accurate statement (though they may very well be) of the average jury verdict in any particular year. Rather, the Working Group found the Jury Verdict Research data useful for purposes of showing the trend in jury verdicts over the last decade. In this regard, it should be noted that the service has used the same basic methodology since well before the relevant reported years. Moreover, while there are different estimates of average jury verdicts for particular areas and years, a number of other sources that have collected such data -- including the Institute for Civil Justice -- corroborate the overall trends reported by Jury Verdict Research, Inc.

34/ This percentage increase is consistent with a survey of California Superior Court medical malpractice verdicts. That survey shows the average medical malpractice award as increasing from $152,970 in 1975 to $649,210 in 1983, a 324% increase. American Medical Association Special Task Force on Professional Liability and Insurance, Professional Liability in the '80s (October 1984). Because the $250,000 cap in California on awards for non-economic damages in medical malpractice cases was only recently affirmed as constitutional (see Chapter 4), it is unclear what effect, if any, the cap has had on malpractice verdicts in California. It is worth noting, however, that the recent insurance problems for medical malpractice have been far less serious in California than in many other states, and that in California the insurance crisis primarily has affected areas other than medical malpractice (e.g., municipal liability).

35/ This remarkable increase is also reflected in the Institute for Civil Justice study of civil jury verdicts in Cook County, Illinois. For example, the average wrongful death award in Cook County increased (in constant dollar terms) from $166,000 in 1970-74 to $336,000 in 1975-79, a doubling over roughly half a decade. M. Peterson, Compensation of Injuries: Civil Jury Verdicts in Cook County 54 (1984).

CHART D

AVERAGE MEDICAL MALPRACTICE JURY VERDICT

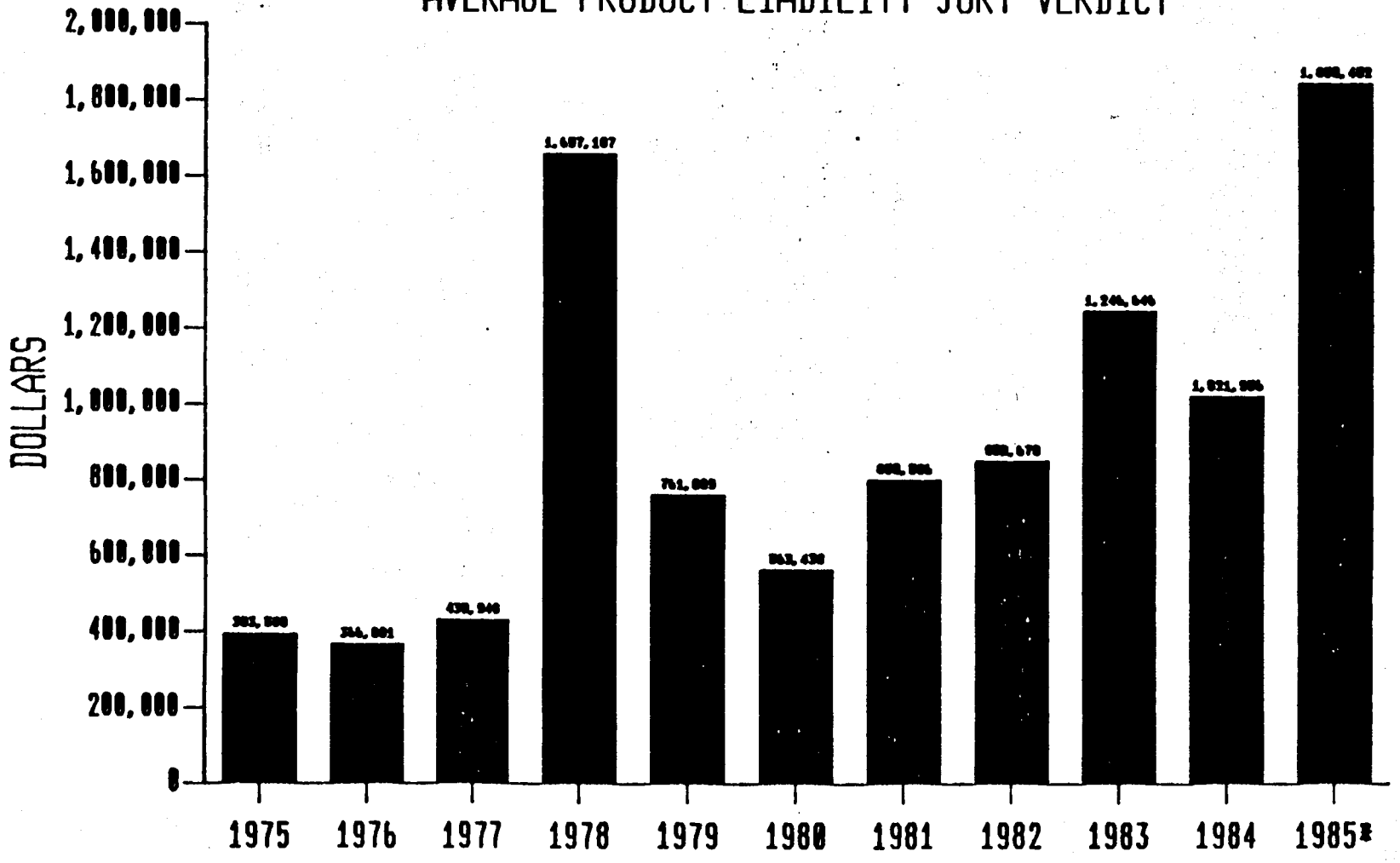


Source: Jury Verdict Research, Inc.

* 1985 Information Not Complete

CHART E

AVERAGE PRODUCT LIABILITY JURY VERDICT



Source: Jury Verdict Research, Inc.

* 1985 Information Not Complete

million-dollar medical malpractice verdicts and 86 million-dollar product liability verdicts (see Chart F), an increase of over 1200% in the number of such verdicts. 36/ If these million-dollar verdicts are deleted, the increase in average verdicts is reduced sharply. For example, the increase in the average medical malpractice jury verdict from 1975 to 1985 drops to 26% and the comparable average product liability verdict jury increase is 87%. 37/ This clearly suggests that the explosion in damages has come largely at the high end of the awards scale.

The Jury Verdict Research data is of only limited value on the absolute number of million-dollar payments, since in all likelihood the vast majority of such payments are through settlements rather than verdicts. The data is highly relevant, however, in that it shows that the percentage rate of increase of verdicts is far higher for large verdicts than for small or medium-size verdicts. Since a significant distinguishing factor between large verdicts and small or medium-size verdicts is that large verdicts tend to be composed to a far greater extent of non-economic damages, 38/ this strongly suggests that non-economic damages play a major role in the explosive growth in large verdicts (as compared to the much more moderate growth in small and medium-size verdicts).

While it is not possible to quantify precisely how much particular elements of damages have contributed to this explosion, it appears that non-economic damages are a substantial factor. Such damages include non-pecuniary compensatory damages for intangible injuries such as pain and suffering and mental anguish, as well as punitive damages. Such non-economic damages are inherently open-ended and subjective, and, therefore, easily susceptible to dramatic inflation. Of interest in this regard is a recent preliminary study by the Institute for Civil Justice which indicates that the average punitive damage award in Cook County, Illinois, increased from $63,000 in 1970-74 to $489,000 in 1980-84 (see Chart G). 39/ Of

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36/ Jury Verdict Research, Inc., supra. The trend toward million-dollar verdicts is also documented by the Institute for Civil Justice. M. Shanley & M. Peterson, Comparative Justice: Civil Jury Verdicts in San Francisco and Cook Counties, 1959-1980 26-30 (1983).

37/ Jury Verdict Research, Inc., supra.

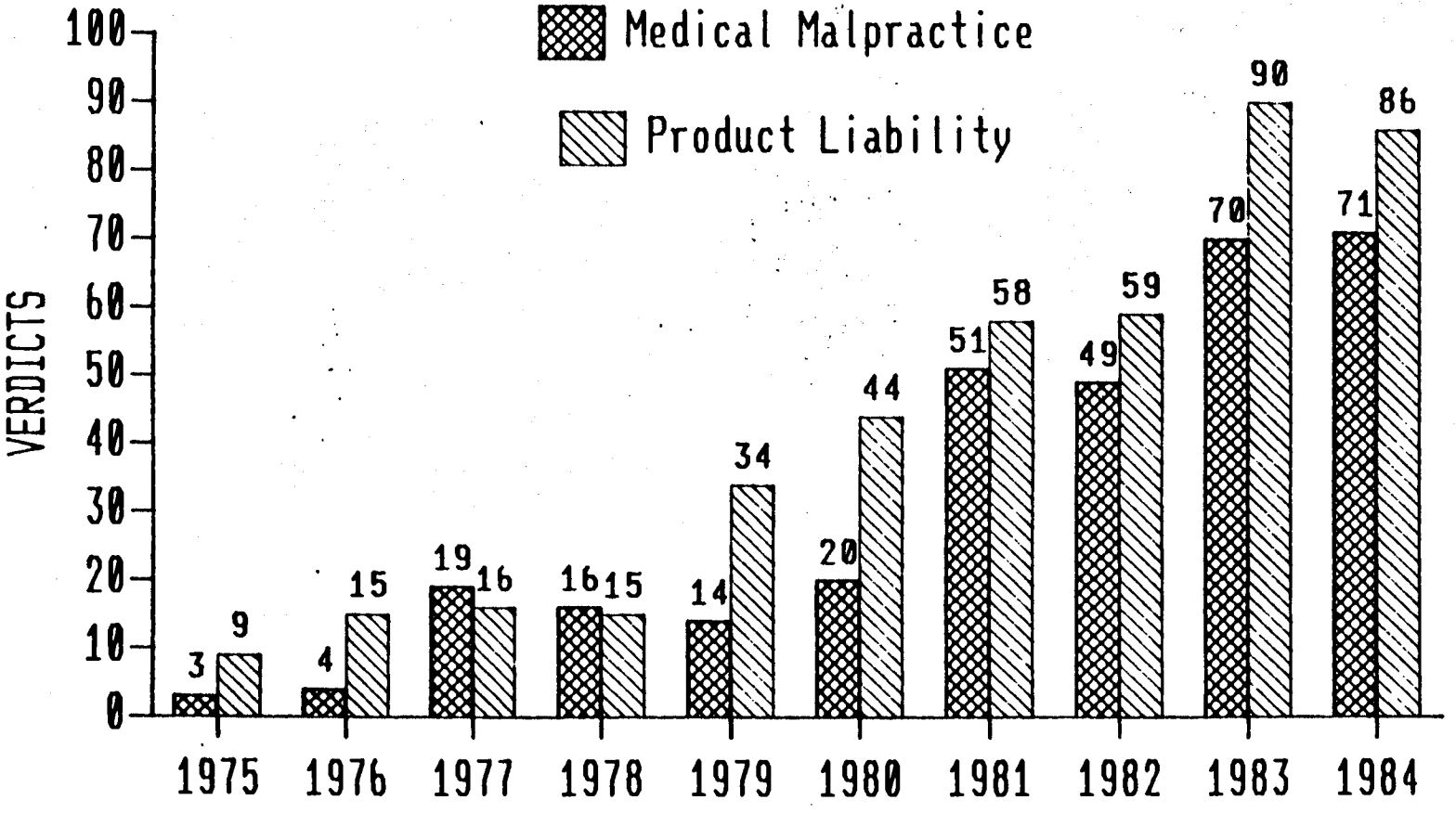
38/ H. Manne, Medical Malpractice Policy Guidebook 138-39 (1985). The study shows that for medical malpractice awards between $100,000 and $200,000, non-economic damages account for approximately 27% of the total award, while for awards above $600,000, the non-economic share increases to 54%.

39/ M. Peterson, Punitive Damages: Preliminary Empirical

(CONTINUED)

CHART F

MILLION DOLLAR JURY VERDICTS

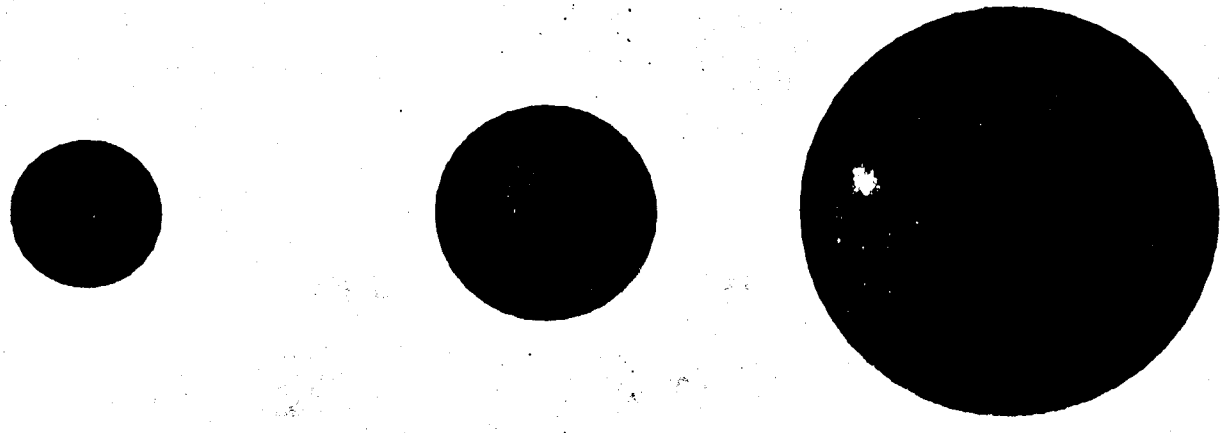


Source: Jury Verdict Research, Inc.

CHART G

AVERAGE PUNITIVE DAMAGE AWARD IN COOK COUNTY*

$63,000 (25 Awards)	$135,000 (39 Awards)	$489,000 (90 Awards)



1970-74	1975-79	1980-84

Source: Institute for Civil Justice

*1984 Dollars

particular interest is that the average Cook County punitive damage award in personal injury cases increased from $40,000 in 1970-74 to $1,152,174 in 1980-84 (see Chart H). 40/

This explosion in damage awards, particularly in the case of non-economic damages, is vastly in excess of the rate of inflation over the comparable period. 41/ For whatever reasons, tort damage awards have suddenly soared in the United States without any apparent justification.

Excessive Transaction Costs

Another serious problem of the tort system is its extraordinarily high transaction costs. A study by the Institute for Civil Justice of the asbestos litigations shows that out of every dollar paid out by the asbestos manufacturers and their insurers as a result of the asbestos litigation, 62 cents on the verage is lost attorneys' fees and litigation expenses (see Chart I). 42/ This does not include the transaction costs borne by the courts in adjudicating these claims.

It also is worthwhile viewing the transaction costs from the

39/ (FOOTNOTE CONTINUED)

Findings 13 (1985). These averages were adjusted for inflation and are stated in terms of the 1984 dollar. The study's analysis of punitive damage awards in San Francisco also showed an increase in such awards, though of lesser magnitude than in Cook County.

40/ Id., at 25 (also adjusted for inflation). Peterson notes that personal injury punitive damage awards in Cook County between 1980-84 amounted to over half of all punitive damages awarded in all case categories by Cook County juries from 1960-84.

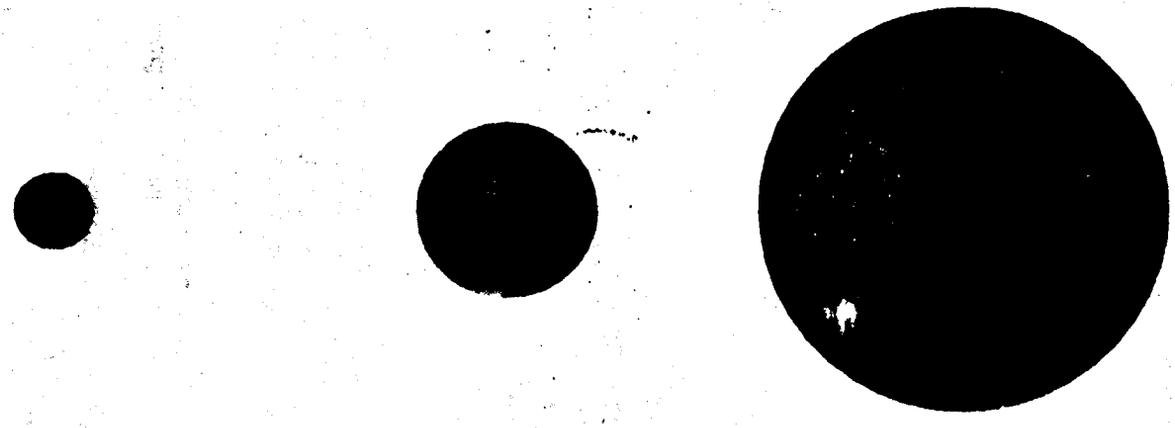
41/ For purposes of comparison, one dollar in 1985 had approximately half the buying power of one dollar in 1975.

42/ J. Kakalik, P. Ebener, W. Felstiner, G. Haggstrom & M. Shanley, Variations in Asbestos Litigation Compensation and Expenses xviii (1984). These costs, of course, include both plaintiffs' and defendants' litigation expenses. In comparing the costs attributable to defendants' litigation expenses to the costs attributable to plaintiffs' litigation expenses it is useful to remember that defendants incur such costs whether or not they prevail, and, indeed, may incur substantial costs defeating even clearly frivolous claims. Measurements of plaintiffs' litigation expenses (such as in Chart I), reflect only those cases in which plaintiffs prevail, while defendants' litigation expenses include all cases, whether or not plaintiffs prevail.

CHART H

AVERAGE PERSONAL INJURY PUNITIVE DAMAGE AWARD IN COOK COUNTY*

$40,000	$217,000	$1,152,000
(5 Awards)	(6 Awards)	(23 Awards)



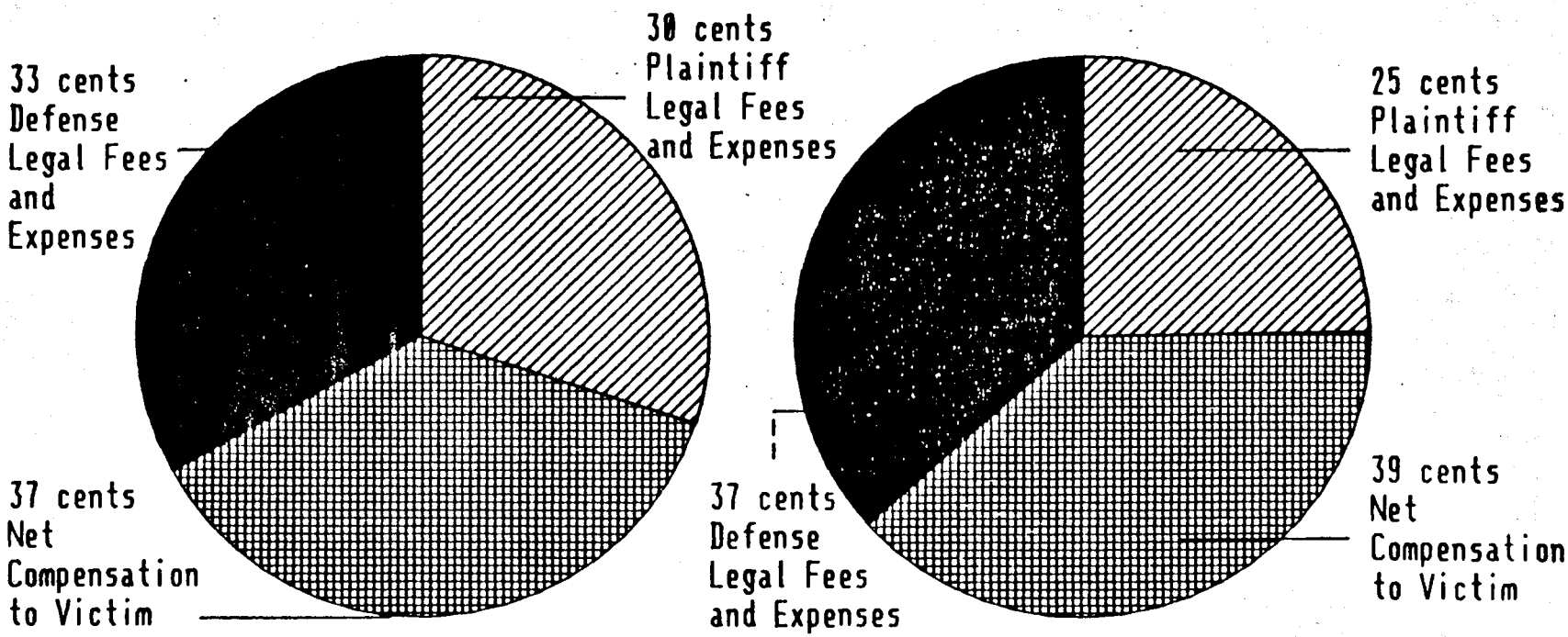
1970-74	1975-79	1980-84

Source: Institute for Civil Justice

*1984 Dollars

CHART I

ALLOCATION OF EVERY DOLLAR PAID OUT IN ASBESTOS CLAIMS



Source: Institute for Civil Justice

perspective of the prevailing plaintiff. The study also shows that for every dollar awarded to plaintiff, 34 cents on the average is lost to legal fees and an additional 5 cents is lost to legal expenses. 43/ In some cases, legal fees alone amounted to as much as 45% of plaintiff's award. 44/

It is difficult to justify such extraordinary transaction costs. But it is particularly difficult to justify such costs when the costs often are borne largely by the seriously injured and by consumers who ultimately must pay for these costs through higher prices for goods and services. The only clear beneficiaries of this system appear to be lawyers.

II. BURGEONING TORT LIABILITY AS A MAJOR CAUSE OF THE INSURANCE AVAILABILITY/AFFORDABILITY CRISIS

The above discussion describes a tort system that in recent years has dramatically increased in scope. One way of measuring that increase is in terms of the increase in the number of tort lawsuits and in the level of damages awarded in such lawsuits. While the available data is limited, and by no means perfect, it clearly confirms that there has been a substantial increase in recent years in both the number of tort lawsuits and awarded damages.

The growth in the number of product liability suits has been astounding. For example, the number of product liability cases filed in federal district courts has increased from 1,579 in 1974 to 13,554 in 1985, a 758% increase (see Chart J). 45/ There is no reason to believe that the states courts have not witnessed a similar dramatic increase in the number of product liability claims.

A similar trend can be found in medical malpractice, where claims 46/ filed against physician-owned companies increased from 10,568 in 1979 to 23,545 in 1983, a 123% increase in four

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43/ Id., at 84. For tried claims, these costs increase to 39 cents and 6 cents respectively. Id.

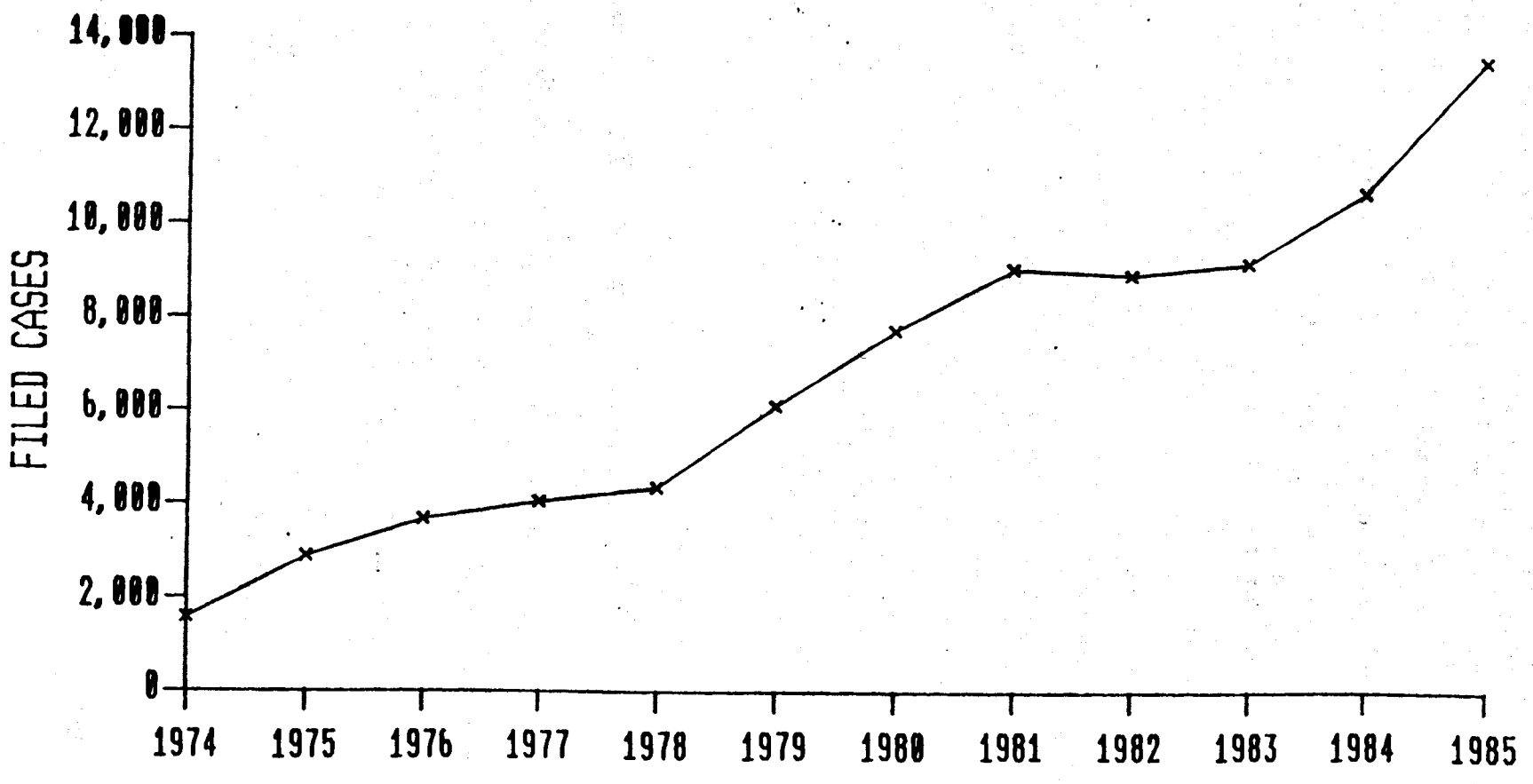
44/ Id. With legal expenses of 5%, prevailing plaintiffs in such cases receive only half of the awarded verdict.

45/ Administrative Office of the United States Courts.

46/ Claims do not, of course, translate directly into lawsuits, since most claims are resolved prior to the filing of litigation. But a substantial increase in claims almost certainly means a corresponding substantial increase in litigation.

CHART J

PRODUCT LIABILITY CASES FILED IN FEDERAL DISTRICT COURT



Source: Administrative Office of the United States Courts

years. 47/ The number of medical malpractice lawsuits per 100 physicians more than doubled from 1976 to 1981, and for obstetricians/gynecologists actually tripled during this period. 48/ In federal courts, which contain only a fraction of all medical malpractice claims, such claims have increased almost three-fold in the last decade (see Chart K). 49/

A similar increase can be found in claims filed against municipal and county officials. A survey of over twelve hundred local governments found that such claims had increased by 141% between 1979 and 1983. 50/ Tort claims against municipalities also have increased dramatically in recent years. For example, New York City witnessed a 375% increase from 1977 to 1985 in personal injury claims, with a corresponding 345% increase in average settlement cost. 51/ The City's long-term liability for tort claims already filed is projected to be $1.5 billion. 52/

The explosive growth in damages over the past decade has already been related in detail. Suffice it to say that the increase in the average tort award appears to have outpaced even the extraordinary increase in the number of such lawsuits. The extent of some of these increases are difficult to comprehend. For example, one verdict reporting service found that the average jury verdict in personal injury lawsuits had increased by approximately 25% or more in three separate years (24.5% in 1980, 30.49% in 1981 and 27.54% in 1983). 53/ The average annual increase in such awards since 1975 has been over 15%. 54/ A subcategory of damages that dramatically illustrates this development is the average jury verdict for the wrongful death

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47/ American Medical Association Special Task Force on Professional Liability and Insurance, Professional Liability in the '80s 6 (November 1984).

48/ H. Manne, Medical Malpractice Policy Guidebook 18 (1985).

49/ Administrative Office of the United States Courts.

50/ Wyatt Co., Public Officials Liability Insurance: Understanding the Market (1986), page 22 (the provided 1984 data is incomplete, see pages 9-10, and therefore is not used for comparison).

51/ Statement by Mayor Edward I. Koch before the Governor's Advisory Commission on Liability Insurance, Feburary 21, 1986.

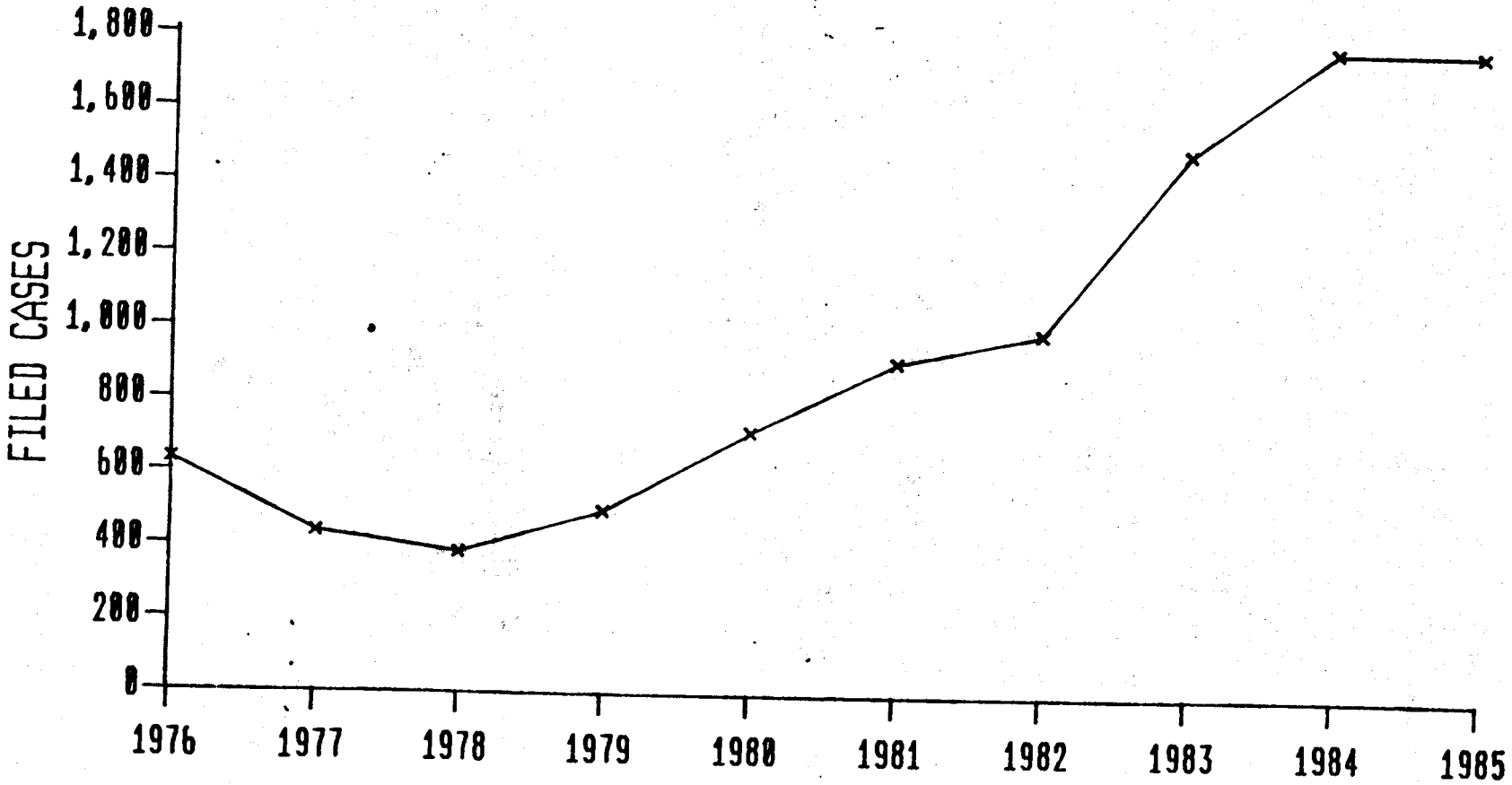
52/ Id.

53/ Jury Verdict Research, Inc., supra.

54/ Id. This is more than double the average annual CPI increase during the same period. Id.

CHART K

MEDICAL MALPRACTICE CASES FILED IN FEDERAL DISTRICT COURT



Source: Administrative Office of the United States Courts

of an adult male. The average award increased from $223,259 in 1975 to $946,140 in 1985, a more than four-fold (324%) increase in ten years (see Chart L). 55/

The increase in the number of tort lawsuits and the level of awarded damages 56/ (or settlements) in and of itself has an obvious inflating effect on insurance premiums. To illustrate, assuming all other factors are held constant, 57/ if the number of lawsuits against a company or person doubles in ten years, and if the average damage award (or settlement) doubles over this same period, that company or person will experience at least a four-fold increase in insurance premiums over those ten years. As noted above, however, for both medical malpractice and product liability the last ten years have witnessed much more than a doubling in lawsuits and average awards.

The above observation leads to an important but troubling insight into the current insurance availability/affordability crisis. Some have speculated that the crisis is the result of the attempt by the insurance industry to recoup losses resulting from its underpricing in the late 1970's and early 1980's. If this theory is correct, then it would seem likely that as such losses are recouped, premiums would decline. The above analysis, however, suggests that while the insurance industry may have underpriced its product for a period of time, the current explosion in premiums results in large part from the fact that now that the insurance industry is facing substantial underwriting losses, it must price coverage to reflect the actual risks presented by tort law. In other words, for a variety of reasons, the insurance industry appears to have kept prices constant or engaged in price reductions in a period during which the risks generated by tort liability increased

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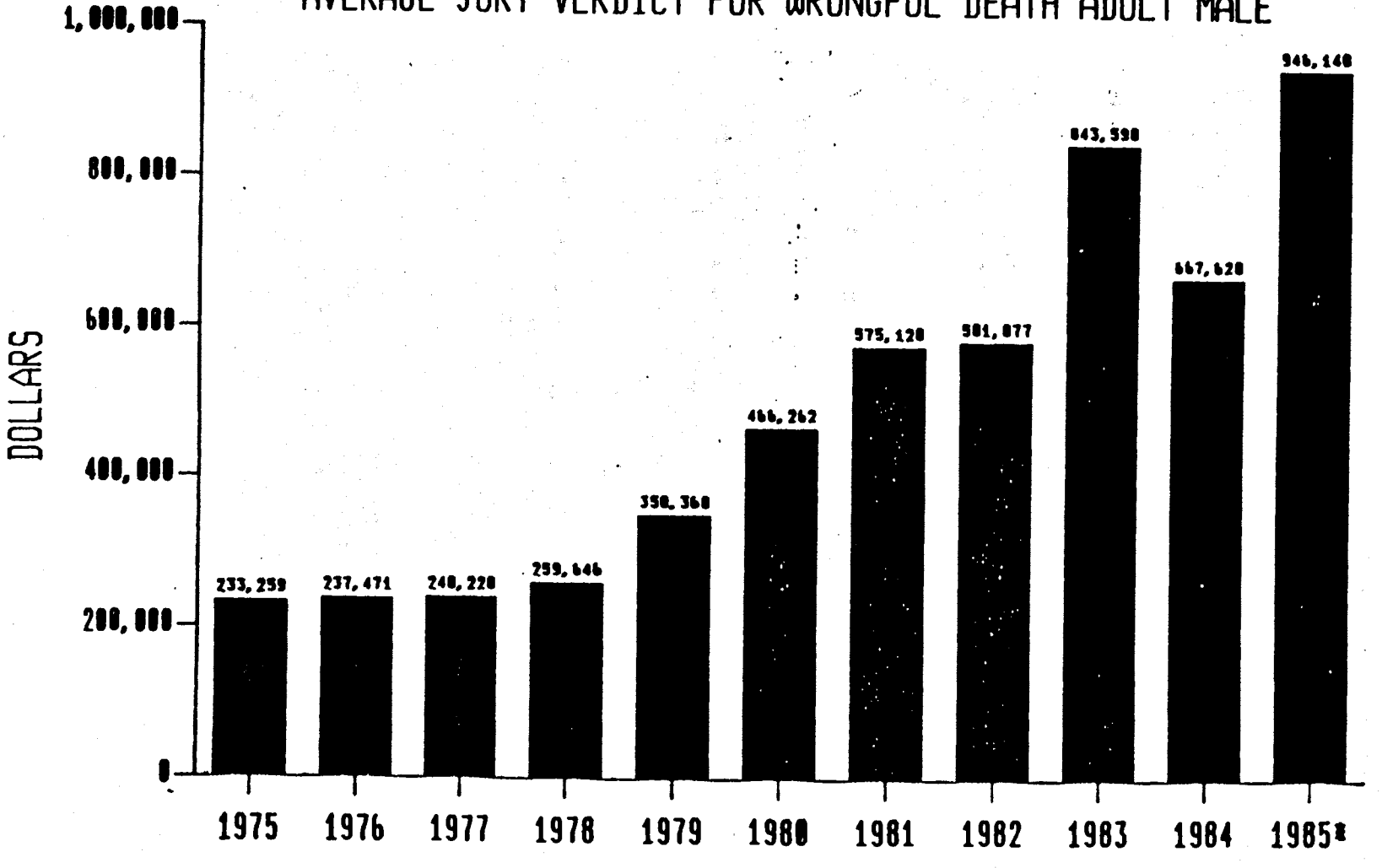
55/ Id.

56/ Jury verdicts, of course, represent only the tip of the claims resolution process. Most claims are resolved before trial. However, settlements by their very nature reflect the range of verdicts available to the plaintiff. Thus, as jury verdicts skyrocket, so do settlements. Settlements also reflect the plaintiff's likelihood of success. As tort law becomes more and more favorable to plaintiffs -- particularly in reducing or even eliminating plaintiff's burden of showing fault or causation -- settlements further increase. Accordingly, in addition to the obvious effect on settlements of increasing jury verdicts, liberalized standards of fault and causation increase the percentage of claims resolved favorably to plaintiff and increase the size of settlements.

57/ Of course, all factors are not held constant. For example, if there is an increase in the percentage of claims resolved favorably to plaintiffs, premiums would have to be increased correspondingly.

CHART L

AVERAGE JURY VERDICT FOR WRONGFUL DEATH ADULT MALE



Source: Jury Verdict Research, Inc.

* 1985 Information Not Complete

dramatically. Now that the industry is attempting to match premiums to risk, there appears to be a dramatic, pent-up increase in premiums to bring premiums back into line with rapidly growing liability risks.

The above analysis, if correct, is troubling in that it suggests that even after the insurance industry's underwriting profitability is restored, premiums are likely to remain relatively high. That is, while the more extreme availability problems may be resolved once the industry controls its underwriting losses, affordability problems may remain as a long-term fixture absent significant reforms of tort law.

There is, however, another important contribution of recent developments in tort law to the availability/affordability crisis which goes beyond the number of lawsuits and size of damage awards. The changing standards of liability and causation have generated tremendous uncertainty. The "rules of the game" of tort liability have changed so dramatically and rapidly in recent years that few are willing to speculate on what those rules will be even a few years hence. Invariably, however, those rules seem to have been changed to the prejudice of parties with pockets sufficiently deep to bear increasingly generous awards of compensation.

This uncertainty as to what the rules of tort liability applicable to any particular company, person or activity will be in future years makes it extremely difficult for the insurance industry to assess risk (and establish appropriate premiums) with any degree of confidence. This undoubtedly exacerbates the affordability problem, and may be a major factor underlying the availability problem. Simply put, insurance, like other business activities, operates most efficiently within a stable legal regime. Tort law, unfortunately, over recent years has been anything but stable.

The recent explosion in tort liability and the lack of legal certainty is a particularly noxious combination that seems to react almost synergistically in promoting the insurance availability/affordability crisis. The rapidly accelerating growth in both the number of tort lawsuits and the size of damage awards in and of itself significantly increases future liability risks. But that risk is magnified by the perception -- based in large part on the lack of a stable legal regime -- that this accelerating growth will continue unabated. The insurance industry thus appears to be extrapolating the massive liability surge of recent years into the future, and seems to be setting its rates in part on the assumption that the on-going deterioration of tort law will continue for some time. Simply put, assessments of future liability risks reflect not only the recent rapid growth in such risks, but the perceived likelihood

that past excesses will be outpaced by the excesses yet to come. 58/

In conclusion, the current problems of tort law can be summarized as follows:

- Too many defendants are found liable (or forced into settlements) where there should be no liability, either because they engaged in no wrongful activity, or because they did not cause the underlying injury.

- Damages have become excessive, particularly in the area of non-economic damages such as pain and suffering, mental anguish and punitive damages. And,

- Transaction costs are far too high.

The ways in which these aspects of the tort system are contributing to the current insurance availability/affordability crisis can be summarized as follows:

- The private sector is being asked to carry a compensation burden which in some instances it simply cannot afford to carry without substantial economic dislocations. Thus, even where insurance is available, in order to carry this compensation burden, it often is priced at unacceptable levels.

- The affordability/availability problem is greatly exacerbated by the lack of a stable legal regime which would allow the insurance industry to assess liability risks with some degree of confidence.

58/ A recent Administration study of the childhood vaccine industry, for example, found that uncertainty as to tort liability was a major factor underlying the severe insurance availability problems facing the industry and jeopardizing the childhood vaccination program. See the Report of the Working Group on Vaccine Supply and Liability (April, 1985).

CHAPTER 3

RECENT INSURANCE INDUSTRY DEVELOPMENTS

The insurance availability/affordability crisis has led both the insurance industry and its customers to consider various changes to the ways in which liability risks are insured. The following is a description of the most significant of these developments and their immediate implications.

I. COVERAGE CHANGES

One of the most important of these changes has been the development of new commercial policy forms by the Insurance Services Office ("ISO"), the statistical and rate-making organization for the property-casualty industry. While these new forms have been filed with each state insurance department, most states have not yet acted on the new submissions.

These new policy forms are more limited in scope than the old forms in that they are written on a claims-made basis and permit certain coverages to be excluded entirely.

Claims-Made Policies

General liability insurance, including product liability coverage, traditionally has been written on an occurrence basis; that is, the policy applies to all injuries and damages that occur during the policy period irrespective of when claims are presented. Under claims-made coverage, the policy covers injuries and damages which occur during the policy period and for which claims are filed during the policy period.

The ISO submission provides that a policyholder can purchase unlimited tail coverage (the period during which claims are covered after termination of the policy) for a cost of up to 200% of the original premium. In addition, a five year extended claims reporting period for known claims is provided for situations where no other insurance is applicable. There is still disagreement over the reinstatement of aggregate policy limits for tail coverage and the effect of defense cost inclusions.

A claims-made policy covers claims occurring after the "retroactive date," ordinarily, the inception date of the policy. Under some circumstances, insurers will be permitted to advance the retroactive date, necessitating the purchase of tail coverage for incidents occurring during the prior period. The retroactive date may be advanced when: (1) there is a change of insurer, (2) there is a change in the insured's operation, (3) if the insured fails to inform the insurer of risks he knew or should have known about, or (4) with the consent of the insured.

The ISO has indicated that it does not intend to limit the use of claims-made policies to specific problem areas such as long-tail or latent injury exposures.

The claims-made forms have not yet been approved by the states, and twelve states have expressly disapproved them as filed. The ISO is working with the Insurance Commissioners to resolve differences.

The insurance industry has indicated that it wishes to use claims-made policies. In general, 1986 is viewed as a transition year during which insurers will train their personnel in the use of the new policy forms and adapt their computers to accommodate the changes. Insurers have indicated that in states where the new forms are not insured, they may use non-admitted subsidiaries or surplus lines carriers to provide the coverage to their clients on claims-made basis for large complex risks and risks in "volatile" classes, or else simply not provide coverage to those risks.

Claims-made policies and other limited coverages also are being adopted by reinsurers. Lloyd's of London has introduced a new claims-made form, as have Weavers and Trenwick American Reinsurance. Each policy is somewhat different. Trenwick, a United States reinsurance company, has stated that it will not write any general liability reinsurance on an occurrence basis after January 1 of this year. Trenwick also has written a claims-made form for use by its ceding companies for "difficult" risks. Other reinsurers have indicated they would reinsure both occurrence and claims-made policies, but would strongly encourage the use of claims-made for heavy casualty risks. As indicated in Chapter 1, some businesses already have been asked to take claims-made coverage for their excess limits coverage. Because of the many different claims-made forms currently being used, this is likely to cause gaps in coverage.

Laser Endorsements

The ISO policy form also includes "laser endorsements" which can be used to limit coverage. These provisions permit an insurer to exclude claims from a specific incident, product or period of time. Several Insurance Commissioners have objected to this provision and stated that, at a minimum, it should be revised to require the signature of the insured indicating an awareness of the exclusion. The inclusion of a laser endorsement would necessitate either the insured's purchase of tail coverage for that product or incident, or the insured's "going bare" for that liability.

Pollution Exclusion

Both the new ISO and Lloyd's of London claims-made commercial general liability policies specifically exclude pollution

coverage. Traditionally, the general liability policy has included the business community's liability for damage caused by the "sudden and accidental" discharge of toxic substances. Environmental Impairment Liability ("EIL") policies are used to cover damages from gradual pollution incidents. In a number of highly controversial cases, courts have expanded the meaning of "sudden and accidental," causing insurers to be liable for EIL-type (gradual pollution) coverage when it was not intended under the policy.

As a result, insurers currently are reluctant to provide any pollution coverage, though Lloyd's of London has indicated a willingness to cover some liability at additional cost on a "named peril" basis only.

Defense Cost Inclusion

Ordinarily, the costs of defending against liability claims are not included within the aggregate limits of the commercial general liability policy. Insurers traditionally have controlled the defense of claims against their insureds by engaging defense counsel and by governing the vigor with which a claim is challenged. The insurers paid all costs, and the full amount of the policy limits were available to pay any settlement or judgment against the insured.

During the product liability crisis of the mid-1970's there were a number of allegations that insurers were, in fact, fueling the claims situation by settling too quickly in many cases that the insureds believed should have been more vigorously contested. As a result, many companies insisted that their insurance contracts include a right to at least partial, if not full, control of defense strategy.

In the mid-1980's, defense costs have escalated rapidly, mostly because of the cost of attorneys' fees, and possibly, in part because of the insureds' desires to contest claims to the fullest degree possible.

In order to control costs, the ISO had proposed to change the commercial general liability form to include defense costs within the aggregate limits of the policy. This practice already is incorporated in at least some other policy forms. 1/

1/ Business Insurance, December 9, 1985, page 1.

The proposal brought a sharp response from insureds, the bar, and the Risk and Insurance Management Society, a trade association of risk managers and insurance buyers. They believe that there will be cases of defense costs exceeding the limits, leaving no money to pay a settlement or judgment. Some are concerned that defense counsel may urge settlement of unworthy claims in order to prevent defense costs from exhausting all available coverage. Others believe that there will be a spate of bad faith claims against insurers when the policy limit is used for legal costs and the insured is left liable for damages.

In response to the concerns of insurance customers, regulators and brokers, the ISO has revised its proposal so that up to 50% of the aggregate limits may be spent on defense costs before the policy limits will begin to be reduced by those expenses. An endorsement will be available so that up to 300% of the limit may be spent on defense costs before the policy limit is affected. A discount will be applied if the policyholder buys less than the 300% endorsement. Insurers apparently will have the option to apply an endorsement which will charge all defense costs to the policy limits. 2/

At its annual meeting in December, the National Association of Insurance Commissioners passed a resolution urging states not to approve the ISO proposal until the proposal can be studied by the Commissioners. The ISO, which had hoped to initiate the defense cost change in July of 1986, will postpone filing its request with the states until at least February 15, 1986. 3/

II. ALTERNATIVE INSURANCE MECHANISMS

As liability insurance becomes unavailable or unaffordable, means of liability protection outside the conventional insurance markets increasingly are being sought and used.

2/ Business Insurance, December 16, 1985, page 1.

3/ Business Insurance, December 23, 1985, page 1.

Insurance Company Creation (Captive or Other)

One response available to large companies unable to buy the insurance coverage they need is to set up their own insurance company. Thirty-three major United States companies recently have established an offshore insurer, A.C.E. Insurance Company, which began operation in November, 1985, and provides up to $150 million in liability coverage. Founding companies include IBM, GE, U.S. Steel and Chase Manhattan, as well as other companies. While A.C.E. offers coverages not available elsewhere, its policies are available only to large companies since it only pays claims exceeding $100 million.

In addition, it recently was announced that a group of fifteen chemical and petrochemical companies are creating a company called CASEX, which would provide excess limits coverage for products, directors and officers, and sudden and accidental pollution liability.

Another group of fifty United States banks are creating a mutual insurer, Bankers' Insurance Co., Ltd., to provide directors and officers liability coverage and bankers blanket bonds.

During the medical malpractice crisis in the early to mid-1970's, groups of medical professionals unable to obtain malpractice coverage formed their own companies, commonly known as bedpan mutuals, to handle their claims. Such insurance groups currently provide about half of the coverage in the malpractice liability market.

Self-Insurance

Some industry groups and trade associations, as well as municipalities in several states, have joined together to self-insure as groups, and others have been able to set up a formal self-insurance program just to handle their own claims. 4/

Self-insurance, either individual or group, also has been a useful vehicle for municipalities for which insurance has become either unavailable or unaffordable.

One major problem encountered by firms seeking to set up self-insurance programs is that reserves for self insurance are not

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4/ A formal self-insurance program is different from "going bare" in that the former sets up reserves to cover claims and treats it similar to an insurance system whereas the latter simply hopes claims do not occur, which may cause financial difficulties if and when they do occur.

accorded the same tax treatment as insurance company reserves, in that self-insurance reserves are fully taxable. While this presents no problem for municipalities and other tax-exempt entities, it is a major hurdle for private entities.

Small firms are generally unable to establish a meaningful self-insurance program individually, but may benefit from group self-insurance if no other insurance is available.

Product Liability Risk Retention Act Groups

The Risk Retention Act ("RRA"), 15 U.S.C. § 3901 et seq., was intended as a mechanism to (1) create an alternative product liability insurance market, and (2) provide a means for smaller insurance buyers to purchase general liability insurance -- including product liability coverage -- as groups. The RRA evolved from an intensive interagency study of the product liability "crisis" in the mid-1970's. President Reagan signed the Act in September 1981, noting that it was a "marketplace solution" to provide product manufacturers, distributors and sellers with affordable product liability insurance.

A Risk Retention Group ("RRG") is formed by any number of product sellers as an insurance company licensed to operate under the laws of any state. The RRG may provide only product liability and completed operations coverage to its members. (Completed operations is work performed by a contractor or product manufacturer installing its product.) The RRG may sell insurance in any state without meeting the licensing or other regulatory requirements of any state other than its domicile. No state may discriminate against an RRG, but states may impose normal premium taxes and enforce compliance with unfair claims settlement practices statutes.

The Act is restrictive in that it limits a RRG to products and completed operations coverage, but permits the establishment of a domestic group captive that is able to do business countrywide.

A Purchasing Group ("PG") may be formed to negotiate for a group policy from any insurer to cover product liability completed operations, and commercial general liability when either of the first two coverages are included. The PG and any entity providing services to the PG are exempt from any state law which would prohibit the PG from purchasing this coverage on a group basis.

A group of companies purchasing together presents an attractive premium base with lower administrative costs to the insurer. In a tight market small companies are subject to cancellation or sharply higher prices because an insurer may prefer to use its

resources on a few large risks. The provisions for purchasing groups was necessary to overcome statutes and regulations in about forty-four states which prohibited so called "fictitious groups" set up for the purpose of buying property or casualty insurance on a group basis.

Very few companies have used the RRA to date, but the rapid change in market conditions likely will lead to a much greater interest in its provision.

One reason that the RRA has been little used is the fact that it is limited to products and completed operations coverages, although groups may include other coverages as long as products is the primary purpose. It is a useful means of expanding insurance capacity, and would provide additional capacity in the alternative market if the products limitation were removed.

III. STATE REGULATORY DEVELOPMENTS

State legislators and insurance regulators have recognized the severity of the liability insurance crisis, and have responded in a variety of ways. One state has barred cancellation or non-renewal of policies and prohibited any increases in the cost of policies in effect. Several other states are considering similar actions. The National Association of Insurance Commissioners adopted a resolution opposing mid-term cancellations and short notices of non-renewal. Other states are implementing or considering the use of Market Assistance Programs, which are voluntary assigned risk pools designed to take risks such as day care centers on a rotating or shared basis. Yet other states are considering joint underwriting associations in which the state regulator mandates the sharing of certain risks

Half the states have "file and use" rate regulation in which the insurance department is notified of a rate increase which becomes effective without action by the regulator. Many of these states reportedly are rethinking their systems because of the sharp increases in the rates of some of the problem lines of coverage.

Regulators normally have viewed commercial insurance as transactions between knowledgeable buyers and sellers, and, accordingly, have refrained from interfering with the market's operation. The recent concerns expressed by the Insurance Commissioners is a measure of the depth of the availability/ affordability crisis, and may foreshadow a heightening in the regulatory "oversight" of commercial insurance.

CHAPTER 4

TORT LAW REFORM

As discussed in Chapter 2, two primary areas have been the focus of the Working Group's examination into the crisis in liability insurance availability and affordability: the current economic difficulties of the insurance industry; and, the extraordinary growth in tort liability in recent years. For the reasons discussed in Chapter 2, while it seems likely that the insurance industry will be able to work its way out of its present economic straits, it is very unclear -- if not doubtful -- that this will significantly alleviate the crisis in insurance availability and affordability. Early indications are that insurers will continue to avoid areas that present a high risk of tort liability, or, where they do provide insurance, will demand high premiums. That is, while the more extreme aspects of the availability crisis may be resolved once the industry regains its desired level of profitability, it appears unlikely at this time that the high premiums that have led to serious affordability concerns will be reduced significantly.

For these reasons, as well as for the other reasons discussed in Chapter 2, there appears to be little that can or should be done by the federal or any other government to "remedy" the economic factors that underlie the current availability/affordability crisis. The excesses of the tort system, however, present a very real opportunity to address a major cause of the insurance crisis with sensible and appropriate reforms. And while some of the changes in the insurance market currently under contemplation (see Chapter 3) probably will relieve some availability/affordability problems, it seems unlikely that these changes will provide long-term, systemic relief without fundamental reforms of tort law.

The following is a list of eight tort reforms that would bring a greater degree of rationality and predictability to tort law, and thereby significantly assist in resolving the availability/affordability crisis. This is by no means an exhaustive list of possible tort reforms. Nor does the accompanying discussion of these reforms indicate how they necessarily should be implemented; that is, on the federal or state level, or through legislative or judicial modification of the law. Rather, this list identifies eight recommended tort reforms which if implemented should return tort law to a credible fault-based compensation system that provides a fair and reasonable level of compensation to deserving plaintiffs through a more predictable and affordable liability allocating mechanism. While these reforms undoubtedly will be resisted by some, they in fact are quite modest and should not dramatically alter the basic principles of tort law as those have existed for centuries.

Recommendation No. 1: Retain fault as the basis for liability.

For the reasons discussed in Chapter 2, fault should be retained as a basis for tort liability. As noted there, fault is the only mechanism in tort law for distinguishing desirable from undesirable conduct, and is an indispensable predicate to many other aspects of the tort liability system without which the system would generate arbitrary and unfair results.

For non-product liability cases, negligence should remain the applicable standard of liability. Strict product liability should under no circumstances be extended outside the traditional area of product injuries. Thus, theories which would apply strict product liability to landlords or to professionals providing services (e.g., pharmacists, architects, etc.) should be strongly resisted and expressly rejected. The trend in some states 1/ to extend strict liability doctrines outside the area of product injuries is a highly pernicious development which will significantly undermine the ability of those sectors of our economy to function properly.

Strict product liability in its traditional sense represents a sensible application of fault-based liability to the realities of modern industrial life. The Working Group, accordingly, does not recommend the abolition of strict product liability, provided the doctrine is kept within its traditional bounds. Unfortunately, strict product liability has been subject to extensive abuse that often has had the effect of transforming the doctrine in practice into absolute liability.

The following are the elements of a strict product liability standard which does not present an impossible or unfair burden to plaintiffs in demonstrating fault on the part of defendant-manufacturers, while at the same time not establishing a scheme of absolute liability which simply uses the manufacturer as an insurer for all risks of injury.

- Liability should be predicated on the existence of a defect which is found to make the product unreasonably dangerous.

- Defendants should only be held liable for uses of a product that are both reasonable and foreseeable. Liability should not be predicated upon unreasonable or unforeseeable alterations of a product that cause the injury, particularly where such alterations are prohibited or warned against. (Alterations, in this regard, can include the failure to provide required and reasonable safeguards, maintenance or inspections.)

1/ See in this regard the recent opinion of the California Supreme Court in Becker v. IRM Corp., 38 Cal.3d 454, 698 P.2d 116 (1985), extending strict product liability to landlords.

- Manufacturers should not be liable for defects which have been the subject of an adequate warning or which are readily apparent to the reasonable consumer. Manufacturers should only be required to warn with regard to uses of a product that are both reasonable and foreseeable.

- Manufacturers should only be held to the state of the art in existence at the time of manufacture of the product. Manufacturers should not be held liable for unknown or unknowable hazards.

The above elements, if applied in a principled manner, should ensure that strict product liability will serve to compensate persons injured as a result of a manufacturer's fault, while preventing that liability doctrine from simply being used as a risk spreading mechanism designed to operate as a product-based insurance scheme.

Recommendation No. 2: Base causation findings on credible scientific and medical evidence and opinions.

One of the most pernicious developments in tort law has been the extent to which causation findings are based on fringe scientific or medical opinions well outside the mainstream of accepted scientific or medical beliefs. Increasingly, juries are asked to make difficult decisions about highly complicated issues of science and medicine. Unfortunately, the personality and demeanor of expert witnesses often may be more critical in making such determinations than decades of evolving scientific and medical investigation and thought.

This problem has resulted in the growing perception that the tort system often is wholly arbitrary in allocating liability in cases involving difficult issues of science and medicine. This is a particularly problematic situation in toxic tort and drug liability cases. 2/

There are a variety of reasons for this problem:

- Many judges do not have the training or inclination to understand complicated scientific and medical concepts, and are unwilling or unable to devote the time and energy needed to educate themselves in a complex body of knowledge.

- In order not to deprive plaintiffs of their opportunity for compensation, many courts allow plaintiffs to take

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2/ For example, see the discussion of Johnson v. American Cyanamid Co., infra.

whatever scientific or medical views they may have -- however incredible -- to the jury.

- Many in the legal system do not appreciate how credible scientific and medical views develop, and the degree to which legal decisionmaking is a poor vehicle for developing such views.

- There often is an understandable frustration with the fact that science and medicine frequently cannot offer the kind of certainty that the legal decisionmaking mechanisms strive to obtain.

The inability of the tort system to deal credibly with complicated scientific and medical issues strikes at the very heart of the ability of tort law to deal with the growing number of cases involving highly complicated scientific and medical issues. While there are no easy answers, there are several remedial actions that the Working Group recommends:

- Greater deference must be paid to government agencies and certain private institutions that have devoted decades of attention and millions of dollars to researching and trying to assess the value of medical and scientific developments. Where such agencies and institutions have determined that particular products, services or techniques are safe or socially beneficial, courts should tread very carefully in overruling those judgments through the vehicle of tort law. Lay juries are a very poor mechanism for second-guessing the judgment of established mainstream scientific and medical views. Other legal mechanisms for determining those views, such as rulemaking and licensing proceedings, generally are far superior in making credible determinations involving complicated issues of science and medicine.

- Courts must be more aggressive in determining the credibility of scientific and medical evidence and opinions before trial, and not simply allow parties to present any theory to the jury. Appellate courts, in turn, should give trial courts greater latitude in making such decisions in early stages of litigation. Judges, where feasible, should receive training on basic methods of scientific, medical and statistical analysis so that they can make such determinations. If necessary, impartial masters with appropriate training should be used for this purpose.

- Studies and opinions that have not been subjected to the peer review process should be presumed invalid. Where peer review has taken place, judges (or masters, where appropriate) should acquaint themselves with the results of such review.

- Courts must learn to accept the reality of uncertainty. They must understand that the fact that some degree of uncertainty always exists does not mean that every scientific or medical belief is as credible as the next. Judges and legislators must not try to "force" scientific certainty where such certainty simply is not possible. Attempts to do so through burden-shifting, presumptions or by requiring agencies to issue scientific "findings," simply create a misleading and deceptive gloss of scientific certainty that in fact does not exist. 3/ Ultimately, the legal system must accept the fact that some things are unknown, and, given existing methods and data, perhaps unknowable for the foreseeable future.

Recommendation No. 3: Eliminate joint and several liability.

One of the most troubling problems in tort law arises from injuries caused by multiple tortfeasors. Historically, such cases were handled by bringing separate actions against each defendant; joint and several liability only existed where concert-of-action was shown (see discussion in Chapter 2). Further, under the doctrine of contributory negligence, a negligent plaintiff could not recover damages from any defendant. Such an approach seemed harsh where plaintiffs were only minimally at fault for their own injuries. Eventually, and in part to remedy the harshness of the old rule, the doctrines of comparative fault and joint and several liability were developed to make it easier for plaintiffs to obtain compensation.

Comparative fault operates to assure that each party, including the plaintiff, is liable for its own fault. Joint and several liability, although originally applied to situations where concert-of-action was shown, is now in many cases applied to all defendants, regardless of their connection to the injury. Comparative fault, when coupled with the doctrine of joint and several liability, allows plaintiffs to recover the entire judgment from "deep pocket" defendants -- even if such defendants are only found to be minimally at fault. Joint and several liability thus frequently operates in a highly inequitable manner -- sometimes making defendants with only a small or even de minimis percentage of fault liable for 100% of plaintiff's damage. Accordingly, joint and several liability in the absence of concerted action has led to the inclusion of many "deep pocket" defendants such as governments, larger corporations, and insured entities whose involvement is only tangential and who probably would not be joined except for the existence of joint and several liability.

3/ As noted, the Working Group does not believe that scientific uncertainty can be handled simply by requiring government agencies to issue pronouncements of risk or causation for which there in fact is no credible basis.

Another problem area is the relationship of joint and several liability to "enterprise" or "market share" liability. See Sindell v. Abbott Laboratories, 26 Cal.3d 588, 607 P.2d 924, cert. denied, 449 U.S. 912 (1980). In theory, "market share" liability such as that established in the California Supreme Court's seminal opinion in Sindell attempts to allocate liability for a generic product (e.g., DES) among various producers on the basis of their share of the relevant market. Even assuming such an allocation is reasonable, 4/ some jurisdictions have devised variations of or alternative approaches to Sindell which apply joint and several liability among the producers of a generic product. 5/ See, e.g., Abel v. Eli Lilly & Co., 418 Mich. 311, 343 N.W.2d 164, cert. denied, 105 S.Ct. 123 (1984); Collins v. Eli Lilly Co., 116 Wis.2d 166, 342 N.W.2d 37 (1984). 6/ The difficulties plaintiffs face in attempting to show which manufacturer of a generic product was responsible for plaintiff's injury in fact can be (but are not always) substantial. While the Working Group does not advocate one approach over another, it firmly believes that any allocation of liability on the basis of market share should limit a manufacturer's liability to its specific share, and that such liability should not, in the absence of actual concerted action, be joint and several in nature.

The Working Group thus recommends elimination of joint and several liability, except in the limited circumstances where the plaintiff can demonstrate that the defendants have actually acted in concert to cause plaintiff's injury. 7/

4/ Because of a number of problems and inequities associated with Sindell, only a few states have embraced the position of the California Supreme Court. See Schwartz & Mahshigian, "Failure to Identify the Defendant in Tort Law: Towards a Legislative Solution," 73 Calif. L. Rev. 941 (1985).

5/ It is unclear whether even Sindell is a true "market share" allocation decision, since under Sindell plaintiff must only sue manufacturers representing a substantial share of the market, and may allocate all liability among those defendants in proportion to their respective market shares.

6/ Particularly disturbing are decisions such as Abel which appear to distort the principles of concerted action to impute concerted action to manufacturers of a generic product.

7/ Joint and several liability as discussed in this report should not be confused with the legislatively enacted schemes for allocating financial responsibility for the cost of cleanup of hazardous waste sites and spills under the Nation's environmental laws, and, in particular, under the Superfund Act

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Recommendation No. 4: Limit non-economic damages to a fair and reasonable amount.

Non-economic damages such as pain and suffering, mental anguish and punitive damages are inherently open-ended. 8/ They are entirely subjective, and often defy quantification. For example, in many instances it simply is not possible, no matter how much money is awarded, to compensate someone fully for the pain and anguish of the loss of a loved one or from a serious injury. Moreover, because such damages are essentially subjective, awards for similar injuries can vary immensely from case to case, leading to highly inequitable, lottery-like results. Accordingly, such damages are particularly suitable for a specific limitation.

The open-ended nature of such damages makes them a particular problem from the standpoint of achieving predictability. Unlike economic damages (medical expenses, lost earnings, etc.), which can be reviewed objectively and thus can be predicted within a given range, non-economic damages are entirely subjective and unpredictable.

Non-economic damages also can serve as a significant obstacle in the settlement process. Plaintiffs and defendants often can

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7/ (FOOTNOTE CONTINUED)

(the Comprehensive, Environmental Response, Compensation and Liability Act of 1980) and the Resource Conservation and Recovery Act (RCRA). Unlike the tort system, which is intended to compensate injured persons and to deter wrongful conduct (see Chapter 2), Superfund and RCRA represent a legislative choice to allocate the cost of these programs among those who contributed to the problems the programs are designed to remedy. Thus, Superfund and RCRA liability, like the liability established under other environmental laws, are founded upon congressional objectives which provide that those who contributed to the problem or profited from the manufacture which created the waste, ought to bear the cost of cleaning it up. Those whose specific contribution to the site can be identified and severed from the whole are not jointly liable under this scheme. Without some degree of joint and several liability under Superfund and RCRA, the effective enforcement of these programs could be seriously impeded as a result of protracted and costly litigation among responsible parties over the precise allocation of cleanup costs.

8/ There are two types of non-economic damages: compensatory (pain and suffering, mental anguish, etc.) and punitive (sometimes called exemplary damages). The latter are designed purely to punish the defendant.

agree quickly on the amount of economic damages, but disagree sharply on non-economic damages. Plaintiffs frequently have unrealistic expectations of non-economic damages in the hundreds of thousands or millions of dollars to which defendants simply are unwilling to agree. Plaintiffs thus often reject settlement offers that from the standpoint of compensation for economic damages are quite reasonable. Plaintiffs' attorneys also often see high non-economic damage awards as necessary to justify high contingency fees, which may lead them to press for a high non-economic damage award when it may be in their clients' interest to obtain a quick and fair settlement.

Nevertheless, plaintiffs should be entitled to reasonable compensation for their pain and suffering and mental anguish. The key in this regard is to provide such compensation, but to ensure that it will be kept within reasonable bounds.

The Working Group believes that $100,000 would be such a reasonable limitation. In this regard, it should be noted that only a handful of claims involve non-economic damages in excess of $100,000. For example, it is estimated that only 2.7% of all medical malpractice claims (5.6% of all paid medical malpractice claims) receive non-economic compensation in excess of $100,000. 9/ However, in those medical malpractice cases going to verdict where non-economic damages above $100,000 are awarded, the non-economic damages award averages between $428,000 and $738,000 (the latter figure being the "best estimate"). 10/ For such awards including non-economic damages in excess of $100,000, on the average 80% of the total award is for the non-economic damages component of the award. 11/ Since the non-economic damages in excess of $100,000 awarded in these cases (including verdicts and settlements) account for between 28% and 50% of all paid out medical malpractice damages, the non-

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9/ H. Manne, Medical Malpractice Policy Guidebook 132-48 (1985). In comparison, approximately half of all claims that end in a jury verdict in favor of plaintiff include a non-economic damages award in excess of $100,000. Id. This suggests that non-economic damages are a major factor in forcing claims to trial.

As discussed in Chapter 2, the Guidebook was prepared for the Florida Medical Association. Henry Manne served as the general editor, and the analysis on the effect of a $100,000 cap was prepared by Patricia Danzon -- "perhaps the most widely known and published economist in the country on the subject of medical malpractice." Id., at 10.

10/ Id.

11/ Id. In this regard, it is worth noting that non-economic damages as a percentage of overall damages increases substantially as the overall damages increase. Id., at 138-39. See discussion in Chapter 2.

economic damages payments in excess of $100,000 alone account for up to half of all medical malpractice damages. 12/ Thus, a $100,000 limitation on non-economic damage awards would affect only a relatively small percentage of all claims, but would introduce substantial predictability into the tort system. 13/

It also is necessary to deal with punitive damages. While some thought was given to an absolute ban on punitive damages, or perhaps a separate limitation, the Working Group concluded that the best approach would be to include punitive damages within the $100,000 limitation on all non-economic damages. Nevertheless, punitive damages should only be awarded for willful conduct bordering on a criminal violation. Specifically, the Working Group recommends that an award of punitive damages be predicated on a demonstration of actual malice.

Even if these recommendations are adopted, punitive damages at best have a tenuous basis in tort law. Increasingly, there has been growing skepticism among legal scholars about the role of punitive damages, 14/ and numerous instances of extraordinary

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12/ Id. The best estimate of the Guidebook is that pain and suffering awards above $100,000 account for nearly 39% of all medical malpractice damages.

13/ Some states have struck down such limitations on constitutional grounds, primarily on the basis of equal protection, on the theory that it is unfair to limit the recoveries of certain plaintiffs (e.g., medical malpractice claimants) while allowing other plaintiffs to receive unlimited recoveries. Recently, however, both the California Supreme Court and the Court of Appeals for the Ninth Circuit upheld such a limitation for medical malpractice verdicts awarded under California law. See Fein v. Permanente Medical Group, 38 Cal.3d 137, 695 P.2d 665 (1985); Hoffman v. United States, 767 F.2d 1431 (9th Cir. 1985). The Supreme Court refused to hear either case, finding with regard to the former that no substantial federal question was presented. Constitutional concerns such as this, however, can only be sensibly considered in the context of specific legal proposals.

14/ See, e.g., Owen, "Problems in Assessing Punitive Damages Against Manufacturers of Defective Products," 49 U. Chi. L. Rev. 1 (1982); Seltzer, "Punitive Damages in Mass Tort Litigation: Addressing the Problems of Fairness, Efficiency and Control," 52 Fordham L. Rev. 37 (1983); Sugarman, "Doing Away With Tort Law," 73 Calif. L. Rev. 555 (1985); Schwartz, "Deterrence and Punishment in the Common Law of Punitive Damages: A Comment," 56 S. Cal. L. Rev. 133 (1982); Ellis, "Fairness and Efficiency in the Law of Punitive Damages," 56 S. Cal. L. Rev. 1 (1982).

abuses. 15/ Punitive damages add considerable uncertainty, and frequently have very little real deterrent effect because they are awarded years after the offending conduct. In any event, the punishment of misconduct is primarily a function of the public law enforcement system, and should not be a common purpose of private litigation.

Nevertheless, the Working Group does not recommend prohibiting punitive damages in tort cases provided they are included within the limitation on non-economic damages. If this is infeasible, the Working Group recommends that punitive damages be abolished. 16/

Recommendation No. 5: Provide for periodic payments of future economic damages.

Traditionally, a losing defendant is required to pay all of plaintiff's future damages in one lump-sum payment. When damages were within reasonable limits, this generally was not a major problem. But as average damages have skyrocketed into the hundreds of thousands of dollars this has become an increasing burden on the defendant (or defendants' insurers). The Working Group, therefore, recommends that future economic damages be paid periodically. 17/

Allowing defendants to pay for plaintiff's damages periodically has several advantages. First, it gives defendants the ability in some cases to digest major adverse judgments by spacing

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15/ One of the most flagrant examples is the $8 million dollar punitive damage award against the defendant in Johnson v. American Cyanamid Co., (District Court No. 81 C 2470), for its decision to produce the Sabin rather than the Salk polio vaccine. Despite the fact that the defendant had complied in this decision with the well established medical judgment of the United States government and virtually the entire medical community, the jury apparently decided to use punitive damages to overrule this judgment and to force the Sabin vaccine off the market. Ironically, the Sabin vaccine has proven far more effective than the Salk vaccine in combating polio. The case presently is on appeal to the Kansas Supreme Court, and the federal government has filed an amicus brief urging reversal.

16/ It frequently is noted that the deterrent effect of punitive damages could be achieved through a system of civil fines.

17/ Where there is legitimate concern that a particular defendant may not be able to make the periodic payments in future years the court should be empowered to require the defendant to ensure the periodic payment through the purchase of an annuity.

payments out over time, much in the same way that many consumers can afford major purchases by buying on installment. Second, society is benefited by the fact that plaintiffs have a guaranteed stream of income, and cannot deplete their awards within a few years. This sharply reduces the possibility that severely injured plaintiffs eventually will become wards of the state.

An important additional advantage of requiring courts to award damages in terms of periodic payments rather than lump-sum awards is that it uses the market's rather than a court's assessment of the applicable interest rate. Under the existing practice in most states, the trial court determines plaintiff's economic loss over plaintiff's lifetime, and then awards plaintiff the present value of those losses in a lump sum. The interest rate used to make that present value calculation is critical, and can significantly reduce or inflate the lump-sum payment. Frequently, courts in making that calculation use interest rates that bear no reasonable relationship to what in fact is available in the market.

A periodic payment requirement effectively avoids this problem by having the court determine the stream of future economic losses and require defendant to purchase an annuity providing a corresponding stream of compensation (where defendant is sufficiently large, an actual annuity probably would be unnecessary). Under such a procedure, the market determines the appropriate interest rate for calculating the present value of those payments (the present value would equal the cost of the annuity). Since the payments are guaranteed through the annuity, subsequent changes in the interest rate would have no effect on plaintiff's compensation. Defendant, on the other hand, would have the market rather than a judge or jury determine the correct interest rate for assessing the present value of future damages.

Periodic payments, as noted, are not unfair to plaintiffs because the payments would be scheduled to be made as the damages are in fact incurred (that is, as earnings are actually lost, or as certain expenses actually occur).

Because the benefits of such a provision would be relatively limited for smaller awards, the Working Group recommends that periodic payments only be required where the total economic damages award exceeds $100,000.

Recommendation No. 6: Reduce awards by collateral sources of compensation for the same injury.

The collateral source rule prohibits the finder of fact from taking collateral sources of income related to the same injury into account in making an award of damages to the plaintiff. This effectively permits the plaintiff to obtain double recovery of certain components of his damages award.

In an era when collateral sources of income were financed largely by plaintiff himself, the collateral source rule may have been sensible. Today, however, when many collateral sources are provided or subsidized by the government or by third parties (such as employers, who often are required by law to provide certain collateral benefits), the traditional justification is called into question. Increasingly, the collateral source rule simply permits a windfall recovery by the plaintiff.

As to publicly provided collateral sources of compensation, there is no justification for not taking such sources into account in determining plaintiff's ultimate damages. The collateral source rule in such circumstances has the effect of requiring citizens to pay compensation twice -- once as taxpayer, and once as the consumer of the product causing the injury. 18/

The situation is somewhat more complicated in dealing with private sources of collateral compensation, particularly where subrogation is involved. 19/ Where a third party (such as an insurer) is subrogated to plaintiff's claim, the collateral source rule may not in fact result in any double recovery. As a practical matter, however, subrogation often is not a significant consideration in many tort actions. In some areas, such as automobile accidents, subrogation is quite common. In other areas, however, such as medical malpractice, subrogation is far less common.

As to private sources, the best approach appears to be to require collateral sources of compensation related to the same injury to be taken into account as long as a third party is not subrogated to that portion of plaintiff's claim. Further analysis may suggest that elimination of subrogation (that is, simply offsetting all collateral sources against the award, and prohibiting subrogation arrangements) may have a limited effect and be justified on the basis of significant reductions in transaction costs.

While the correct approach to workers' compensation benefits must be considered very carefully, workers should be required to seek their workers' compensation benefits where appropriate. The Working Group takes no position on whether subrogation and indemnification actions between employers and manufacturers

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18/ Another reason to be concerned about such a windfall is that much of the windfall is in fact a windfall for attorneys in the form of attorneys' fees.

19/ In the context of insurance, subrogation allows the insurer to obtain from the tortfeasor-defendant all or part of its payments to the insured-plaintiff arising from the injury caused by the tortfeasor.

found liable as third party defendants should be eliminated, as has been proposed in some legislation. The Working Group will continue to review the merits of proposals dealing with such subrogation and indemnification actions.

Recommendation No. 7: Schedule contingency fees.

Currently, plaintiffs' attorneys receive a flat percentage of their clients' awards, usually between 30% and 40%, but sometimes as high as 50%. Where plaintiff's award is moderate, such a contingency fee may, in fact, be quite reasonable, since the attorney has significant costs and may face substantial risks that must be reimbursed. But as the average plaintiff's verdict has increased in recent years, such a high percentage becomes difficult to justify. Increasingly, there are indications of extraordinary abuses where attorneys receive fees in the hundreds of thousands of dollars for limited work. Particularly in mass liability cases where the groundwork for liability has been laid in previous cases by other attorneys, the fees often bear no relationship whatsoever to the work of or the risk to plaintiff's attorney. 20/

Nevertheless, the Working Group does not recommend, as some have suggested, the abolition of contingency fees. Often, such fees are the only means available to the poor to afford an attorney and obtain access to the legal system. The problem with contingency fees emerges when awards become very high, and a flat contingency rate becomes excessive. The Working Group, therefore, believes that contingency fees should be scheduled to decrease as awards increase.

Specifically, the Working Group recommends the following schedule: 25% for the first $100,000, 20% for the next $100,000, 15% for the next $100,000, and 10% for the remainder. Thus, for an award of $500,000, plaintiff's attorney would receive $80,000 rather than $166,666 (assuming a one-third contingency fee), and for an award of $1,000,000, would receive $130,000 rather than $333,333.

There are a number of justifications for scheduling contingency fees:

- Verdicts often are inflated by judges and juries to compensate plaintiff for what is well understood to be high attorneys' fees. Defendants thus pay for such fees through higher insurance premiums or awards,

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20/ As discussed in Chapter 2, the prevailing plaintiff is not only liable to his attorney for the agreed to contingency fee, but also for litigation expenses. Such expenses often can amount to an additional five to eight percent of the underlying award.

which, in turn, are passed on to consumers through higher prices. It is difficult to justify placing such a burden on American consumers for the purpose of paying what often amounts to exorbitant attorneys' fees.

- Similarly, in order to compensate plaintiffs for very high contingency fees, settlements often are higher than otherwise would be the case. As with high awards, these payments ultimately are passed through to the consumer. More problematic, however, is that attorneys' fees often can become a major impediment to settlements since defendants may balk at paying a higher than justified award in order to compensate plaintiffs for exorbitant attorneys' fees. In such situations, attorneys' fees create an additional burden by causing cases not to be settled that otherwise would be settled.

- Contingency fees also distort the incentives of attorneys. Such fees may lead plaintiffs' attorneys to hold out for high non-economic damages (and, potentially, windfall profits for the attorney requiring only minimal additional work on the attorney's part), while the clients may be best served with obtaining economic damages and more limited non-economic damages as promptly as possible.

- Scheduling contingency fees also should substantially reduce the excessive transaction costs presently plaguing the tort system. This is particularly important in such areas as the asbestos litigations where there are only limited resources available to compensate a large pool of plaintiffs.

In this regard, it is worth noting that the Federal Tort Claims Act contains a 25% cap on attorneys' fees for lawsuits filed under the Act, and a 20% cap on attorneys' fees for settlements obtained under the Act's administrative claims process. 28 U.S.C. § 2678. Violations of these limitations are punishable by fine or imprisonment, or both. A similar 25% attorneys' fee cap (with similar sanctions) is found in the Social Security Act. 42 U.S.C. § 406. None of these caps appears to have had any significant effect on the ability of persons suing the government to obtain adequate legal representation. In fact, the number of lawsuits filed under both the Federal Tort Claims Act and the Social Security Act has increased substantially in recent years.

The Working Group has considered and recommends against the adoption of the English Rule on attorneys' fees, which would transfer attorneys' fees to the losing party. While such a rule might deter some frivolous litigation, it also would inhibit many lawsuits that may be merited but where some preliminary discovery may be necessary to determine the strength of plaintiff's claims. Moreover, because many plaintiffs essentially are judgment proof, the widely held belief that such

a rule would significantly deter frivolous litigation may be largely illusory.

A preferable (but still problematic) alternative approach to the English Rule would be to use a transfer of attorneys' fees as a means of motivating parties to settle their claims at an earlier point in litigation. Thus, a rule modeled on Rule 68 of the Federal Rules of Civil Procedure, 21/ but including attorneys' fees, might be useful. Perhaps the most promising approach would be to combine alternative dispute resolution with a transfer of attorneys' fees.

Recommendation No. 8: Develop alternative dispute resolution mechanisms.

The Working Group believes that alternative dispute resolution holds much promise. Experimentation and experience, however, is the only reliable vehicle for determining which systems will work. Alternative dispute resolution proposals range from binding arbitration to mediation, and include such procedural innovations as mini-trials and expedited discovery techniques. Many of these proposals are worthy of serious consideration, and states represent excellent laboratories in which to develop and explore these various alternative dispute resolution proposals.

The Working Group strongly supports alternative dispute resolution, and believes that the organized bars, legislatures, and jurists should be more receptive to alternative dispute resolution proposals. Where necessary, particularly in areas such as medical malpractice, states should be encouraged to consider seriously the necessary constitutional changes to permit the use of alternative dispute resolution.

The Working Group believes that the most promising use of alternative dispute resolution will be to encourage the early settlement of lawsuits. For example, requiring non-binding arbitration where part or all of attorneys' fees shift to the party which rejects an arbitration award and obtains a less favorable result in litigation, much as costs of litigation are shifted for rejected offers of settlement under Federal Rule of Civil Procedure 68 (see supra), might be an effective means

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21/ Rule 68 ("Offer of Judgment") provides that costs of litigation will shift to a plaintiff who has rejected an Offer of Settlement made under the rule and not obtained a judgment more favorable than the rejected offer. There currently is a proposal under consideration to include attorneys' fees in Rule 68, as well as to make other changes to the Rule. Inclusion of attorneys' fees in Rule 68, however, has a number of serious problems that must be considered very carefully. These and other problems have led the Department of Justice to caution against the proposed changes to Rule 68.

for using alternative dispute resolution to facilitate and expedite early settlements.

The Working Group does not believe, however, that alternative dispute resolution needs to or should involve major changes to the standards of liability or causation in tort law. The merits of alternative dispute resolution are largely unrelated to which standard of liability is used in resolving disputes. The value of alternative dispute resolution lies in procedural rather than substantive changes in the law.

CHAPTER 5

GOVERNMENT INSURANCE: A NON-SOLUTION

The growing liability insurance availability/affordability crisis has spawned calls for government insurance or indemnification for persons or companies unable to obtain adequate insurance coverage through the private sector. For the reasons discussed below, such government insurance or indemnification would be highly undesirable and would do nothing to remedy the problems underlying the availability/affordability crisis.

The most serious deficiency with the various schemes for government insurance or indemnification is, as noted, the fact that such proposals do not address the problems that have led to the availability/affordability crisis. Instead, these schemes simply would pass the costs of the crisis directly to the taxpayer. While it is difficult to estimate the potential cost of such a program to the American taxpayer, it should be noted that the insurance industry suffered an estimated $25 billion underwriting loss in 1985 (see Chapter 2). This loss does not include self-insurance or captive insurer losses, which in all likelihood represent additional billions of dollars.

A government insurance or indemnification program would by definition certainly involve the riskiest activities; that is, those activities that even the insurance industry is unwilling to underwrite. To the extent that the government attempts to address affordability problems by offering coverage more cheaply than the industry, the government, of course, simply would be subsidizing certain purchasers of insurance. Again, the cost of such subsidization is difficult to estimate, but considering that the insurance industry paid out over $126 billion in 1985, with related expenses of $37 billion (see Chapter 2), such a subsidy easily could involve tens of billions of dollars annually. 1/ (Again, these figures do not include self-insurance or captive insurers).

Government insurance or indemnification would not only pass these costs to the taxpayer, but could exacerbate the current problems of the tort system. One of the few constraints left in tort law is the recognition that "deep pockets" are not after

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1/ For example, over recent years the National Flood Insurance Fund has been subsidizing flood insurance by roughly $150 million annually. The cumulative loss for the program to date is approximately $1.4 billion. The President, in his latest budget submission, reiterated his intention to continue to phase out this costly subsidy. The riot insurance program, which existed from 1968 to 1984, was able to sustain itself through collected premiums. The relative success of the program, however, was largely due to the decline in urban riots after the program was instituted.

all bottomless -- that there is a finite amount of resources that can be reallocated through tort liability. Government indemnification or insurance would remove that last restraint, since the resources of the Federal Government are all too often viewed as without limit. Thus, courts and juries might be even more willing to skew liability and causation standards to ensure compensation, and to award the most generous compensation conceivable.

There are, however, a number of compelling reasons for rejecting the concept of government insurance or indemnification other than because of its potential cost and the failure to address the real problems underlying the crisis. Perhaps foremost among those reasons is that such a program would most likely jeopardize among the most effective and important mechanisms currently existing in the private sector to protect public health and safety. The insurance industry plays a vital role in promoting public health and safety by policing insureds to ensure that risks of injury are minimized. Insureds who fail to minimize such risks, or who experience higher than normal claim rates, may find the desired level of insurance coverage more difficult to obtain and more expensive. The insurance industry thus plays an important role in creating incentives that protect public health and safety, both in policing insureds, and in passing the benefits of safety back to the insureds through lower premiums.

While the role of insurance in promoting public health and safety is by no means perfect, and the above description admittedly is somewhat idealized, insurance creates important health and safety incentives which cannot be dismissed lightly. This critical function of insurance is undermined to the extent that the government supplants the private sector in providing insurance or indemnification, particularly for high risk activities. The government, even if and when it demonstrates the best of intentions, simply does not have the resources, experience, flexibility or incentives to replicate the activities of the private sector in policing insureds' practices and setting premiums to reflect claims experience. In addition, were the government to undertake such activities, the existing health and safety bureaucracies almost certainly would prove inadequate. Substantial additional funds, personnel and resources would need to be devoted to these activities, and in many areas new bureaucratic structures would need to be established. 2/ If, as seems likely, such additional investments of government resources are not made, government insurance or indemnification would operate as a clear disincentive to greater safety since insureds would receive

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2/ The necessary collection and analysis of relevant information would of itself be a major undertaking requiring substantial investment of additional government resources.

the benefit of a risk transfer to the government (and, accordingly, would have less incentive to protect public health and safety) without any corresponding checks upon their conduct or activities. Both the consumer and the taxpayer would be the ultimate losers.

To the extent that the government institutes an insurance or indemnification program, such a program also would increase significantly in two ways the involvement of the government in the private sector. First, while the government, as noted, cannot replicate the efforts of the insurance industry, it would have to become involved in the activities it has insured or indemnified to ensure that such insurance or indemnification does not lead to completely open-ended liability on the part of the government. This necessarily would involve new additional forms of government supervision and regulation of private sector activities.

A second undesirable but inevitable effect of such a program would be that the government frequently would be forced to manage, or at least actively oversee, the litigation of cases involving the liability of its insureds, since the insureds often would have only a limited incentive to contest aggressively claims, however meritless, against which they are fully insured or indemnified. Even putting aside the consideration of the massive investment of litigation resources that would be needed by both the insuring agencies and the Department of Justice, this could involve the government directly and actively in some of the most controversial and visible tort litigation in our society, much of which would involve litigation in state court under substantive, procedural and evidentiary rules of state law.

An additional consideration is that such a program necessarily would involve the federal government in state regulation of the insurance industry since such regulation could have a significant impact on the kind of insurance or indemnification the federal government would have to provide. For example, state regulators who might wish to avoid approving politically unpopular rate increases or policy provisions might be far more inclined to withhold such approvals if they perceived the federal government as ready and willing to provide an alternative source of insurance. The federal government, in turn, in order to avoid such wholesale transfers of the insurance burden, could very easily find itself compelled to regulate the insurance industry directly, or to regulate the state regulators. Either way, it would represent a substantial intrusion by the federal government into the regulation of the insurance industry.

Finally, a federal program of insurance or indemnification would interfere with and perhaps severely inhibit the ability of the market to devise new policies, insurance mechanisms, and specific contractual provisions to meet changing economic and

social conditions. Where the current services of the insurance industry prove inadequate or unacceptable, insurers and insureds have strong incentives to restructure those services so that the needs of the marketplace can be met (witness, for example, the current discussions over the introduction of claims-made policies and the inclusion of defense costs). Where government insurance or indemnification is available, however, insureds may be far more inclined to seek such insurance (particularly where it is subsidized, either intentionally or unintentionally) than to negotiate with insurers or invest considerable effort and resources shopping for better conditions. Insurers, in turn, who may feel themselves compelled to offer otherwise unattractive services to customers they wish to retain, may find a government insurance or indemnification program a convenient dumping grounds for the risks they would rather spin-off. 3/ The end result could very well be that the ability of the marketplace to respond to new conditions with innovative solutions could be severely chilled if the "safe harbor" of government insurance or indemnification were available to both the insureds and the insurers. 4/

In sum, government insurance or indemnification would be a highly undesirable and counterproductive response to the current availability/affordability crisis. It effectively would amount to the nationalization of a potentially large portion of one of the Nation's leading financial industries. And, given the history of past government involvement in the private sector, it is all too apparent that removing the federal government from the insurance industry once the purported justification for its presence had passed would be an arduous if not ultimately futile endeavor.

3/ Such risks most likely would include the type of long-latency, catastrophic risks endemic to toxic torts. As is apparent from the asbestos litigations, such insurance would expose the taxpayer to potentially massive liability. The problem of insurers spinning off certain types of business very likely would generate pressure for some form of federal regulation of such practices.

4/ It should be noted in this regard that the contractor indemnification provision which the Administration supports in the context of Superfund reauthorization is purely discretionary in nature, is limited to cleanups under the control of the Environmental Protection Agency, is linked to a critical limitation on liability (liability would be predicated only on negligence), and would be provided only because it will be extremely difficult, if not impossible, to keep this vital program in operation without such limited and closely regulated contractor indemnification (which presumably will include both limits and deductibles).

CONCLUSION

This report contains within it a number of observations, conclusions and recommendations. The most important of these, however, for the purposes of the Tort Policy Working Group, are what this report implies as to the appropriate response of the federal government to the current crisis in insurance availability and affordability. In this regard, the pertinent conclusions are straightforward and relatively apparent.

First, tort law appears to be a major cause of the insurance availability/affordability crisis.

Second, there are a number of beneficial reforms of tort law that the federal government can support and promote in sensible and appropriate ways.

Third, to the extent that other factors -- such as the recent large underwriting losses of the insurance industry -- underlie this crisis, there is little the federal government can or should do to remedy these problems. While the contribution of these economic factors seems clear, it is likely that these problems will work themselves out in the short-term as the insurance industry restores its desired level of profitability, and as other insurance industry developments (see Chapter 3) are implemented. It seems highly unlikely, however, that these changes will substantially alleviate the crisis, particularly the affordability aspect of the crisis, without substantial reforms of tort law.

Fourth, the Working Group found nothing to support the suggestion that this crisis could be remedied through federal regulation of the insurance industry or of state insurance regulators.

Fifth, while a federal insurance or indemnification program obviously could provide subsidized insurance where insurance is unavailable or unaffordable, for many reasons (see Chapter 5) such a program would be highly undesirable and ultimately counterproductive.

In sum, tort law appears to be a major cause of the insurance availability/affordability crisis which the federal government can and should address in a variety of sensible and appropriate ways. But significant, long-term reform cannot and should not come solely from the federal government. Ultimately, state governments and courts must address the current excesses of tort law. Their active participation is essential to finding workable solutions to the increasingly debilitating problems of tort law.

*U.S. GOVERNMENT PRINTING OFFICE: 1986-491-510:40090

Tab F

Tab 53

REPORT OF THE BOARD OF TRUSTEES

Report: BB
(A-88)

Subject: Impact of Product Liability on the Development of New Medical Technologies

Presented by: Alan R. Nelson, M.D., Chairman

Referred to: Reference Committee B
(Betty L. Cottle, M.D., Chairman)

Resolution 6 (A-87), which was adopted by the AMA House of Delegates, calls for a study of the impact of product liability on the availability of drugs and other medical therapies. This report provides an overview of the impact of product liability lawsuits on research and development of vaccines, contraceptives, and other medical therapies, finding that product liability lawsuits are having a profound negative impact on the development and utilization of potentially life-saving medical technologies. The AMA supports continuing the efforts of tort reform.

INTRODUCTION

Product liability is having a profound negative impact on the development of new medical technologies. Innovative new products are not being developed or are being withheld from the market because of liability concerns or inability to obtain adequate insurance. Certain older technologies have been removed from the market, not because of sound scientific evidence indicating lack of safety or efficacy, but because product liability suits have exposed manufacturers to unacceptable financial risks.

The number of cases commenced in federal courts involving product liability generally has increased at a compounded annual rate exceeding 17% over the last 14 years[1] (see Figure 1). From 1974 to 1985 the average jury award in product liability suits climbed from $494,580 to $1,850,452. It is estimated that only one-third of the award goes to the plaintiff; the remainder covers attorney's fees and court costs.

Past House Action: A-87:320

Pharmaceutical manufacturers have been hard hit by product liability suits, especially manufacturers of vaccines and contraceptive agents. The number of lawsuits filed against the manufacturers of DTP (diphtheria and tetanus toxoids and pertussis vaccine), for example, has climbed from fewer than 100 during the three-year period 1982-1984 to 110 in 1986 alone. Current legal interpretation of product liability law, especially the doctrine of strict liability, diminishes the incentives of a manufacturer to research, develop, and produce vaccines.

It has been claimed that the main culprit in skyrocketing liability insurance rates is the insurance industry, which purportedly made imprudent investments in the early 1980s when interest rates were high and now charges exorbitant premiums because the interest rates have dropped.[2] Evidence clearly shows that the profits of the insurance industry vary significantly from year to year, and interest rates are an important determinant of insurance industry profits. A recent study, however, demonstrated that the rise in liability insurance premiums is not due to collusion among insurers, cyclical behavior, or systematic errors in forecasting losses, but to growth in the discounted value of expected liability losses.[3] In the pharmaceutical industry meaningful product liability insurance has all but disappeared. According to one financial analyst in London, "Lloyds and other companies have become very cautious about this type of business in the US because of unpredictability . . . . It has been difficult for them to assess the level of likely claims and hence to price business."[4]

This report will describe the different legal doctrines used in product liability suits and discuss the impact of product liability on the manufacturers of vaccines, contraceptives, and other drugs and devices.

THEORIES OF RECOVERY

Product liability suits typically employ one of three legal doctrines: negligence, breach of warranty, or strict liability. Negligence is a violation of the duty to use ordinary and reasonable care with respect to persons to whom a duty of care is owed. To sue for negligence in product liability, a plaintiff must show that defendant breached his or her responsibility to exercise reasonable care in the design, manufacture, assembly, testing, or inspection of the product or in providing adequate warning concerning the use of the product. A drug manufacturer would likely

be found negligent if a drug was not manufactured in accordance with "current good manufacturing practices," and the specific failure was causally linked to the injury. Currently, most drug and medical device manufacturers follow good manufacturing practices, and few cases of negligence result from defective manufacture, assembly, or testing and inspection of finished products. Most suits invoking the negligence doctrine base their claim on the duty to warn, although, increasingly, plaintiffs allege failure to conduct adequate general safety testing and sometimes improper design.

The duty to warn can be applied in suits invoking either the negligence or strict liability doctrines. Generally, the legal duty is to warn medical professionals, as "learned intermediaries," about the inherent dangers in the use of the product. Learned intermediaries are presumed able to understand the risks and weigh them against the expected benefits to be derived from use of the product and are expected to uphold their fiduciary responsibility to do what is in the best interests of their patients. The concept of learned intermediary has generally relieved manufacturers of responsibility to warn patients directly of the dangers inherent in the use of a drug or medical device. Manufacturers have been held liable, however, if their package inserts, "Dear Doctor" letters, advertising, promotional materials, or the activities of their sales staff provide misleading, insufficient, or ambiguous information on risks associated with the use of the drug and thereby prevent physicians from making informed decisions.

A manufacturer is legally held to the standards of an expert and is responsible for keeping abreast and informing the medical community of newly discovered adverse effects. The adequacy of the warning is generally based on the level of knowledge at the time of the injury. A manufacturer has not been expected to warn of dangers discovered subsequent to the injury, about which they could not have known at the time of the injury.

The scope of liability based on negligence may have been expanded by the case of Toner v. Lederle Laboratories.[5] In this case a young boy was paralyzed from the neck down after receiving the whole cell DTP vaccine. The plaintiff's lawyer alleged that the manufacturer knew how to make a pertussis vaccine that was safer and equally effective but did not pursue development. The attorney for the defense argued that the effectiveness of the split cell vaccine was unproven. The jury held that Lederle was negligent for "failing to design or manufacture a safer vaccine," and returned a $1.13 million judgment for the plaintiff on that basis.

There are two types of warranties, express and implied. The doctrine of express breach of warranty allows recovery from a manufacturer whose product did not conform to an assertion by the manufacturer, when, as a result of that lack of conformance, the plaintiff was injured. Express warranties are based on oral or written statements and can be absolute. For example, if a drug company specifically stated there were no contraindications to a drug but an individual was later shown to have a contraindication to that drug (even if the contraindication was discovered subsequent to the statement), the manufacturer could be liable for breach of warranty. As stated by the courts, "The obligation of a warranty is absolute, and is imposed as a matter of law irrespective of whether the seller knew or should have known of the falsity of his representations."[6] Implied warranties are created by statute and attach to all sales. They attach if the product has been distributed in a truly "defective" state (ie, is not fit for the intended purpose or deviates from similar goods) and if the "defective" product resulted in personal injury. Breach of express warranty is relatively easy to avoid and defend against in comparison to negligence and strict liability, and although breach of implied warranty is still alleged in most cases, it has been displaced in most cases by negligence and strict liability in medical product liability suits.

Strict liability holds a defendant liable for a "defective" product regardless of fault. The plaintiff must simply show that the product was defective or unreasonably dangerous and that it caused physical harm. The public policy rationale behind the doctrine of strict liability is:

> On whatever theory, the justification for the strict liability has been said to be that the seller, by marketing his product for use and consumption, has undertaken and assumed a special responsibility toward any member of the consuming public who may be injured by it; that the public has the right to and does expect, in the case of products which it needs and for which it is forced to rely upon the seller, that reputable sellers will stand behind their goods; that public policy demands that the burden of accidental injuries caused by products intended for consumption be placed upon those who market them, and be treated as a cost of production against which liability insurance can be obtained; and that the consumer of such products is entitled to the maximum of protection at the hands of someone, and the proper persons to afford it are those who market the products.[7]

Almost all states recognize that there are some products, such as prescription drugs and vaccines, that cannot be made completely safe. Manufacturers of unavoidably unsafe products are specifically protected from strict liability by those states that have adopted comment k of the Restatement (Second) of Torts, which states:

> Unavoidably Unsafe Products: There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs. An outstanding example is the vaccine for the Pasteur treatment of rabies, which not uncommonly leads to very serious and damaging consequences when it is injected. Since the disease itself invariably leads to a dreadful death, both the marketing and the use of the vaccine are fully justified, notwithstanding the unavoidable high degree of risk which they involve. Such a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it unreasonably dangerous. The same is true of many other drugs, vaccines, and the like, many of which for this very reason cannot legally be sold except to physicians or under the prescription of a physician. It is also true in particular of many new or experimental drugs as to which, because of lack of time and opportunity for sufficient medical experience, there can be no assurance of safety, or perhaps even of purity of ingredients, but such experience as there is justifies the marketing and use of the drug notwithstanding a medically recognizable risk. The seller of such products, again with the qualification that they are properly prepared and marketed and proper warning is given, ... is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk.

At least one court, however, has held that, under certain circumstances, a drug may not be afforded protection by comment k of the Restatement (Second) of Torts. In Feldman v. Lederle Laboratories[8] the New Jersey Supreme Court stated:

> We see no reason to hold as a matter of law that all prescription drugs that are unsafe are unavoidably so. Drugs, like other products may contain defects that could have been avoided by better manufacturing or design.

Thus, although a drug has been through the rigorous FDA approval process and found by that expert regulatory agency to be safe and efficacious, some courts have decided that it is a jury question as to whether drugs contain "defects" that could have been avoided.

IMPACT OF PRODUCT LIABILITY ON DEVELOPMENT OF MEDICAL THERAPIES

Effect of Product Liability on Vaccine Manufacturers:

Vaccines are one of the great success stories of medicine. Their impact on the prevalence of communicable diseases has been very impressive, and the amount of suffering and pain prevented by vaccines is incalculable. For example, the prevalence of measles dropped from 315.2 per 100,000 population in 1950 to 0.6 per 100,000 in 1983.[9] The number of cases of poliomyelitis dropped from 57,000 in 1952 to 4 in 1984. Smallpox has been eradicated from the world, while diseases such as tetanus, diphtheria, and polio have been extensively controlled. Vaccines are still an extremely important means of preventing the spread of disease and are needed for "herd immunity." In England, when the DTP vaccination rate dropped from 79% in 1973 to 31% in 1978, there was an epidemic outbreak of pertussis.[9]

Vaccines do have some risks. The most serious vaccine-related injuries and their estimated prevalence are shown in Table 1. I in society's interest to adequately compensate vaccinees who are injured by vaccination. The issue is not whether to compensate the injured parties but to determine a method to compensate for injuries directly resulting from vaccination that is fair to the injured, the manufacturer, and society at large.

Until 1986 (see below), the tort system was the only formal setting in which to determine compensation for parties directly injured from vaccination. Successful vaccine liability suits usually were based on a failure to warn. Vaccine manufacturers are considered to have a greater responsibility to warn recipients than do the makers of most pharmaceuticals or medical devices and are generally obliged to ensure that any warnings accompanying their vaccines are actually communicated to the vaccinee rather than simply to the physician. This duty to warn the vaccinee rather than the physician is an exception to the concept of the "learned intermediary". In Davis v. Wyeth Laboratories[10] the courts ruled that, when vaccines are administered at mass immunization clinics, there is no learned intermediary, and it is the "responsibility of the manufacturer to see that warnings reach each consumer, either by giving the warning itself or by obligating the purchaser to give

warning." Subsequent court decisions concluding that vaccination procedures are so routine as to remove the learned intermediary from the process, have expanded the manufacturer's duty to warn to include immunizations in a private physician's office.

In Reyes v. Wyeth Laboratories[11] the federal courts held that, even though the polio vaccine was properly produced and administered, shipped with printed warnings, and there was strong evidence that the disease was caused by an unrelated wild virus rather than by the vaccine, the manufacturer was liable because it should have warned the plaintiff's parents that there was a remote possibility that the vaccine might cause polio. The reasoning was,

> Statistically predictable as are these rare cases of vaccine-induced polio, a strong argument can be advanced that the loss ought not to lie where it falls, but should be borne by the manufacturer as a foreseeable cost of doing business, and passed on to the public in the form of price increases to his customers.

Over the last 10 years the number of liability suits filed against vaccine manufacturers has increased significantly, resulting in vaccine prices that greatly exceed the inflation rate (see Figure 2).

The reluctance of manufacturers to produce vaccines without adequate protection from product liability suits was also exemplified by the swine flu vaccine difficulties during the Ford Administration. In 1976, the CDC forecast a probable outbreak of the swine flu and recommended a national immunization program. Vaccine manufacturers and their insurers refused to produce vaccines for the national program without special protection from liability. According to one insurance executive, "new liability doctrines made the manufacturers uninsurable at any price."[12] Legislation had to be enacted making the United States the sole possible defendant in any action for damages arising out of the swine flu vaccination program. Thousands of claims were filed producing conflicting court decisions that exacerbated the uncertainty prompted by Reyes v Wyeth. The government paid almost $80 million, much of it to people immunized for swine flu who contracted Guillain-Barre syndrome.

Because of product liability concerns and an inability to obtain reasonably priced insurance, several companies, including Wyeth and Parke-Davis, ceased producing childhood vaccines.[13]

More recently, the manufacturer of a vaccine for Japanese encephalitis discontinued its distribution in this country because the firm was unable to obtain liability insurance. Individuals traveling to the rural areas of India, China, Korea, Nepal, Burma, and Thailand may be at increased risk of developing encephalitis because of the withdrawal of this vaccine from the US market.[14]

Considerable concern has been expressed regarding the impact of product liability on the development of valuable vaccines in the future. For example, a headline in Science pointedly questioned "Will an AIDS vaccine bankrupt the company that makes it?"[15] Brian Cunninghan (Vice President and General Counsel for Genentech) stated, "As the law stands today, manufacturers are held liable for injuries caused by a vaccine even though they were not negligent in designing it. In these circumstances, in my opinion, the legal system has simply run amuck. And for a small company like Genentech, we simply cannot take the financial risk."[15] Recently the National Academy of Sciences found:

> Given the extremely high cost of vaccine development programs and the present concerns over liability for vaccine-related injuries, many manufacturers may be unwilling to initiate or pursue the derivation or distribution of a vaccine to prevent AIDS.[16]

The doctrine of a duty to warn is predicated on the assumption that the informed individual has the freedom to weigh the risks against the benefits and to decide whether or not to purchase or use the product.[17] Most vaccinees, however, especially those receiving vaccines required for school entry, often do not have the freedom to reject immunization. Therefore, other forums for compensation of the injured are generally considered necessary. In 1986, Congress passed a bill to provide an alternative environment to settle compensation questions regarding vaccines required for school entry. This grew out of the recognition that the courts are an inappropriate setting in which to settle such questions. The bill did not make its compensation mechanism an exclusive remedy and continues to permit these cases to be brought as lawsuits in the traditional court system. On November 14, 1986, President Reagan signed this legislation into law. The Omnibus Budget Reconciliation Act of 1987 established an excise tax to fund future claims and to authorize appropriations from general revenues to fund preexisting claims. The excise tax, taking effect January 1, 1988, is $4.56 per dose for DTP, $4.44 per dose for MMR, $0.29 per dose for poliomyelitis vaccine (both oral and injectable), and $0.06 per dose for diphtheria and tetanus vaccines.[18]

All vaccines have some inherent risk. However, society has gained tremendously by mass vaccination programs. It would be a travesty to have product liability concerns adversely affect the continued development and utilization of this life saving technology. The no-fault compensation program of 1986, while far from perfect, is a step in the right direction.

Analysis of Contraception Liability:

Contraceptive research and product development has been greatly impeded by product liability concerns. In the early 1970s, there were 13 pharmaceutical companies actively pursuing research in contraception and fertility. Now, only one US company conducts contraceptive and fertility research.[19] Unless the liability laws are drastically altered, it is very unlikely that pharmaceutical companies will aggressively pursue research in this area.

The Director of the National Institute of Child Health and Human Development has expressed concern about this issue:[20]

> Research [is constrained by] a system that becomes driven primarily by concerns over lawsuits. This is already affecting our institute's research program in two ways. First, our ability to test new drugs and devices related to pregnancy has been curtailed because of the inability of some of the investigators we support to obtain liability insurance for the testing at any price. If we cannot do the clinical testing, we cannot bring new products to the public. Second, our ability to conduct research on alternative obstetric practices to what is standard, accepted and safe from a medicolegal standpoint faces constraints based on fear of a malpractice suit if an adverse outcome occurs in the experimental group....When we are forced into a situation where we must follow established dogma rather than be allowed to try something new and possibly better for fear of a malpractice suit, medical research and progress will come to a halt and the health care of our people will suffer. This must not be allowed to happen.

But it may already be happening. In 1986, a landmark case allowed recovery of $4.7 million from Ortho Pharmaceutical Corporation by a woman claiming that her child's birth defects resulted from use of Ortho-Gynol Jelly.[21] This ruling was upheld on appeal in spite of overwhelming scientific evidence that contraceptive gels are not teratogenic. The FDA had previously reviewed the data and concluded that no warning about possible teratogenicity was necessary. The courts allowed the judgment of persons with no medical training to overrule the federal agency which has the responsibility and the medical expertise to ensure that drugs are safe and effective. The appellate court ruled:

> Plaintiffs' burden of proving that Katie Wells' defects were caused by the product did not necessarily require them to produce scientific studies showing a statistically significant association between spermicides and congenital malformations in a large population . . .. [I]t does not matter in terms of deciding the case that the medical community might require more research and evidence before conclusively resolving the question.[22]

This indicates that the courts will now allow as the sole basis for liability anecdotal evidence that is considered unacceptable by the scientific standards of the day[23]. The appellate court stated:

> We recognize, as did the Ferebee court, that a cause-effect relationship need not be clearly established by animal or epidemiological studies before a doctor can testify that, in his opinion, such a relationship exists. As long as the basic methodology employed to reach such a conclusion is sound, such as use of tissue samples, standard tests and patient examination, products liability law does not preclude recovery until a "statistically significant" number of people have been injured or until science has had the time and resources to complete sophisticated laboratory studies of the chemical.[24]

Intrauterine devices have also been under attack from plaintiff lawyers alleging negligence. The manufacturers of all but one IUD have stopped their distribution and sale within the US because of product liability concerns (a second manufacturer of IUDs has recently entered the US market). The Dalkon Shield, manufactured by A.H. Robins, exposed some users to higher than normal risks of pelvic inflammatory disease and infertility. Trial evidence suggests that Robins may have known of the risks uniquely associated with its IUD yet did not inform physicians or the public of the problems. A relatively small number of plaintiff lawyers specialized in handling suits against the makers of the Dalkon Shield and were able to obtain adequate cash flows from out-of-court settlements. However, in 1985 Robins declared bankruptcy, which caused all of the outstanding cases to be consolidated in the bankruptcy courts, halting all settlements and eliminating the source of cash flows for the lawyers. At that point, these same lawyers began focusing their attention on other IUD manufacturers, especially G.D. Searle Company. The number of suits filed against Searle shot up to 800 by 1986, and Searle spent $1.5 million defending the last four trials alone.[25] In January 1986, Searle removed the Cu-7 IUD from the market, citing "unwarranted product litigation" as the main reason for its action. At that time, the total sales for Cu-7 were only $11 million annually. One

study reported that the withdrawal of the Cu-7 and TCu-200 IUDs from the market by Searle and the earlier withdrawal of Ortho Pharmaceutical Corporation's Lippes Loop IUD in September 1985 left an estimated 1.4 million women in need of an alternative method of birth control. This situation may result in an increase of up to 123,000 pregnancies per year.[26]

Analysis of Other Drug and Medical Device Product Liability:

Small drug and device manufacturers, including much of the medical biotechnology industry, are very susceptible to product liability suits and rising liability insurance premiums. It is not surprising, therefore, that a survey discovered that over two-thirds of biotechnology companies consider product liability an important factor to consider when deciding whether to proceed with commercial introduction.[27] Nearly 60% felt that tort reform was needed to limit liability, and over one-third of small and mid-size companies may refuse to bring a product to market unless liability insurance is available. The threat of product liability suits has even halted the distribution of investigational drugs under study. For example, the distribution of Botulinum A toxin, an investigational drug used to treat strabismus and blepharospasm, conditions for which no good alternative therapy exists, had to be halted for many months due to lack of product liability insurance.

One of the most disconcerting movements by the courts is their willingness to ignore overwhelming scientific evidence when determining whether a product was the "proximate cause" of the injury. For example, in addition to the Wells case discussed above, the prescription drug Bendectin was withdrawn from the market not because of scientific evidence of its hazards but because of the large number of lawsuits against the manufacturer. The American College of Obstetrics and Gynecology felt that Bendectin was safe and effective in treating nausea and vomiting of pregnancy. The College stated, "The decision by Merrell Dow [to discontinue the distribution of Bendectin] creates a significant therapeutic gap. Nausea and vomiting during pregnancy cannot always be treated by symptomatic means, and in the past year, severe cases have led to serious maternal nutritional as well as other deficiencies."[28]

In 1987, the FDA developed a new set of regulations in an attempt to get potentially life-saving drugs to desperately ill patients more rapidly. The new regulations, known as the Treatment IND regulations, allow physicians to prescribe selected drugs to patients while the drugs are still in Phase III; occasionally drugs can be distributed late in Phase II trials if the manufacturer is willing to make them available. This new system may remove a regulatory block to improved patient care. The potential of product

liability suits, however, threatens use of the Treatment IND process. A Chief Executive Officer of a major pharmaceutical company has stated, "the product liability specialist could take someone to court and convince a sympathetic jury that the venal drug company in its desire to charge for drugs as soon as possible took advantage of a sick and dying person and deprived him or her of his last few precious weeks on earth."[29]

RECENT CHANGES IN STATE LAWS REGARDING PRODUCT LIABILITY

Nineteen states have enacted new legislation addressing product liability (see Table 2). Some have incorporated provisions specifically protecting drug and device manufacturers. For example, Ohio, Oregon, New Jersey, and Texas provide a defense to punitive damages against a manufacturer if the drug was approved by the FDA and a manufacturer acted with due diligence when any additional risks were reported. New Jersey also established a rebuttable presumption that a warning which has been approved by the FDA is adequate.

CONCLUSION

The AMA recognizes that product liability issues are having a profound negative impact on the development and utilization of potentially life-saving medical technologies. Laws developed to protect the public at large can sometimes hurt the very individuals they were meant to protect. Basic biomedical research is deteriorating in certain fields because product liability inhibits utilizing that research to develop new medical products. Small companies involved in innovative research, such as many of the biotechnology firms, are delaying or foregoing certain product releases because of inability to obtain adequate insurance coverage. Finally, useful products are being taken off the market because the discounted costs of defending litigation and purchasing insurance premiums can sometimes exceed the projected profits for the product.

Patients deserve to receive the best medicine that can be provided. There is a social responsibility to protect individuals from unnecessary harm and to compensate a person when wronged, but there is also a responsibility to protect manufacturers from unjustified liability when, using the best available knowledge, they develop products that, although unavoidably unsafe, offer such benefits that their manufacture and distribution greatly benefits society as a whole. It is particularly important to eliminate tort liability that is predicated not on the manufacturer's unacceptable

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conduct but rather on the injured person's "need" for compensation or the manufacturer's presumed ability to provide that compensation. To do less will jeopardize all citizens, which would be the greatest miscarriage of justice.

RECOMMENDATIONS

The Board of Trustees recommends that:

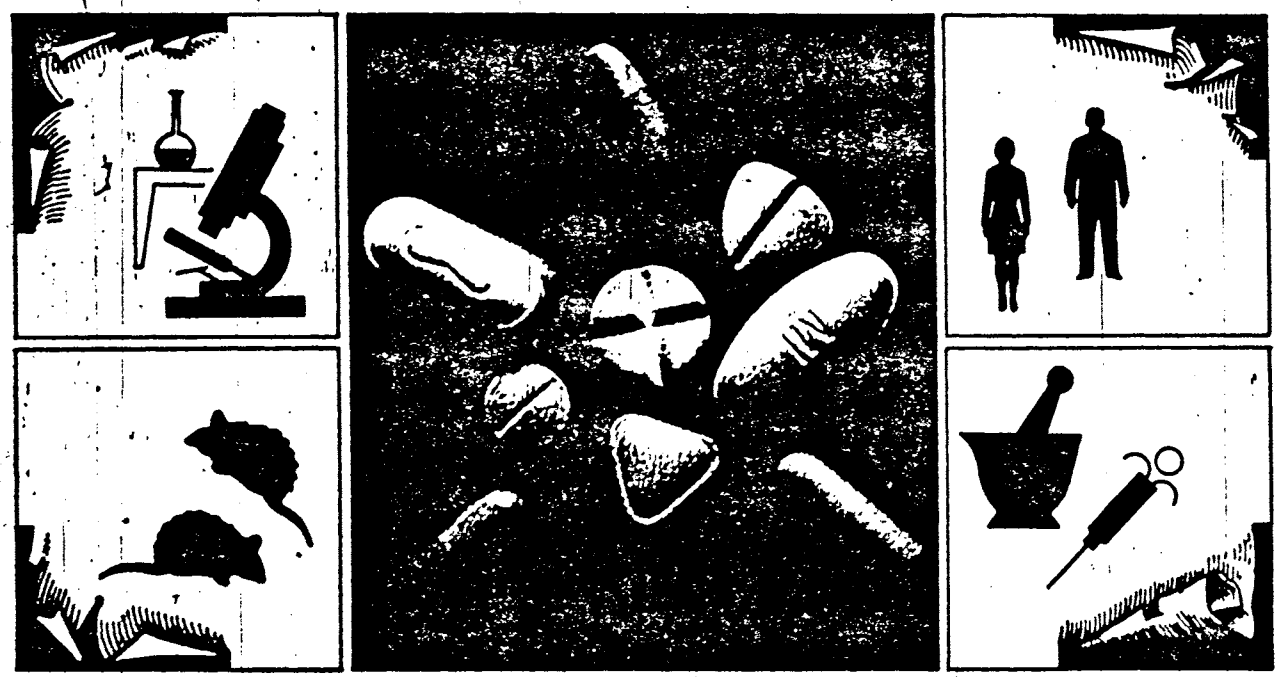
1. The AMA urge the continuation of efforts at the state and federal level to reform product liability form; and

2. The AMA support creative solutions to prevent product liability suits from slowing the development and utilization of medical technologies in this country.

Amended by H.O.D. vote.

The Beginnings: Laboratory and Animal Studies

by Jeffrey P. Cohn



The scene is a typical one. A patient, perhaps you or I, goes to a doctor and gets a prescription. Then a pharmacist fills the prescription, with instructions to take the drug in the prescribed amount and manner over the following days, weeks or months. This scene is repeated millions of times across this country every day—some 1.6 billion prescriptions are filled every year in the United States, an average of seven for every man, woman and child. In fact, the process is so commonplace that the pills, tablets, capsules and other medications that virtually every one of us relies on to restore or maintain good health at some point in our lives come to be taken for granted.

Yet these drugs—and the improved quality of health they bring to the American people—are truly "miracles of modern science." In fact, the process for discovering, developing and testing new drugs encompasses some of the most exciting areas of scientific discovery today. The endeavor runs the gamut from basic biomedical investigation of living cells and molecules to applied research that yields new consumer products to improve health care.

THE CUTTING EDGE

"We are on the cutting edge of the biological sciences," says Rhoda Gruen, a biochemist at Hoffmann-La Roche, Inc., a leading pharmaceutical research and manufacturing firm, headquartered in Nutley, N.J. "We suck up new information like a sponge. Everything we do is subject to change as new scientific information becomes known."

The research process is a complicated, time-consuming, and costly one whose end result is never known at the outset. Discovering a new drug has been likened to searching for the proverbial needle in a haystack. Literally hundreds and sometimes thousands of chemical compounds must be made and tested to find one that can achieve the desirable result without too-serious side effects.

The complexity of the process can be gauged, in part, by the diversity of scientific disciplines engaged in finding new drugs. Traditional organic chemists, physiologists and statisticians have been joined in recent years by new kinds of specialists. Biochemists study the chemistry of life processes. Molecular biologists study the molecules that make up living matter. Toxicologists investigate chemicals' potential for harm. Pharmacologists look at how drugs work. And computer scientists apply the power of their sophisticated machines to analyze and assess new chemicals. Each provides a different way of looking for that needle.

Such a complicated process costs vast amounts of time and money. The Pharmaceutical Manufacturers Association (PMA), a trade group of research-based drug makers, says 10 years or more are needed to study and test a new drug before

the Food and Drug Administration can approve it for the general public. That includes early laboratory and animal testing, the subject of this article, as well as later clinical trials using human subjects. (See page 10.)

Drug companies spend about $65 million, on average, to develop a new drug, says economist Steven Wiggins of Texas A&M University. Actually, Wiggins, who conducted a study on the costs of drug development on behalf of PMA, says the real cost of bringing a drug to market is more like $125 million. That includes what the economists call the opportunity cost of investing money in research whose payoff may be years away, instead of in a more immediate moneymaking venture. A company such as Hoffmann-La Roche, whose annual sales in the United States alone exceeds $1 billion, spends about $2 million each business day on research worldwide.

BUILDING ON GOOD SCIENCE

There is no standard route by which the 2,400 drugs now sold in the United States were developed. "Each drug has its own way of being born," says Clement Stone, senior vice president for Merck, Sharp & Dohme research laboratories, West Point, Pa. "Often we consciously search for a drug for a specific use, but more often it is serendipity. What is required, though, is good science building on good science."

In some cases, a pharmaceutical company decides to develop a new drug aimed at a specific disease or medical condition. In others, company scientists may be free to pursue an interesting or promising line of research. And, in yet others, new findings from university, government or other laboratories may point the way for drug companies to follow in their own research.

Indeed, the process typically combines elements of all three avenues. "We let our scientists do and make use of the best research they can in their fields," says Ronald Kuntzman, vice president for research and development at Hoffmann-La Roche. "The only question we ask as a company is whether this research is leading toward development of a new drug."

New drug research starts by studying how the body functions, both normally and abnormally, at its most basic levels. The pertinent question, Kuntzman says, is: "If I change it [the body's functioning], will I have a useful drug?" That, in turn, leads to a concept of how a drug might be used to prevent, cure or treat a disease or medical condition. Once the concept has been developed, the researcher has a target to aim for, Kuntzman adds.

Gruen elaborates: "Disease processes are complex and involve a sequence of events. If you want to intervene in the disease process, you try to break it down into its component parts. You then analyze those parts to find out what abnormal events are occurring at the cellular and molecular levels. You would then select a particular step as a target for drug development with the aim of correcting the cellular or molecular dysfunction."

A NEW CHOLESTEROL DRUG

Take cholesterol, a wax-like substance found naturally in the body. Too much cholesterol, either naturally or in the diet, can cause it to build up on the inside walls of blood vessels. This can clog the arteries that deliver blood to the heart muscle, blocking the flow of oxygen and nutrients, causing a heart attack.

There have been few drugs that effectively cut cholesterol levels without either toxic or unpleasant side effects. This has limited their use. Others that were tested acted too late in the process by which the body makes cholesterol to lower its levels. What was needed, says Eve Slater, a cardiologist and Merck's director for biomedical research, was a drug that would act earlier in the cholesterol-making process.

To find one, scientists at Merck and elsewhere spent decades studying how the body makes and uses cholesterol. Along the way they identified more than 20 biochemical reactions necessary for the body to make cholesterol, along with the enzymes required at each step to turn one chemical into the next one in the chain.

The research problem, Slater says, was to find the step where interference by a drug would effectively lower cholesterol production. By the 1970s, scientists had found a possibility. They had isolated a chemical, mevalonic acid, that was an early link in the cholesterol chain and an enzyme called HMG-CoA reductase that produced mevalonic acid.

What was needed, then, was a drug that could either inhibit HMG-CoA reductase or prevent cells from correctly using the enzyme.

Sometimes, scientists are lucky and find the right compound quickly. More often, Gruen says, hundreds or even thousands must be tested. In a series of test tube experiments called as- says, compounds are added one at a time to enzymes, cell cultures, or cellular substances grown in a laboratory. The goal is to find which show some chemical effect. Some may not work well, but may hint at ways of changing the compound's chemical structure to improve its performance. The latter process alone may require testing dozens or hundreds of compounds.

COMPUTER CLUES

A more high-tech approach is to use computers to simulate an enzyme or other drug target and to design chemical structures that might work against it. Enzymes work when they attach to the correct site on a cell's membrane. A computer can show scientists what the receptor site looks like and how one might tailor a compound to block an enzyme from attaching there.

Nevertheless, "computers give chemists clues to which compounds to make, but they don't give any final answers," says Kuntzman. "You still have to put any compound you made based on a computer [simulation] into a biological system to see if it works."

Yet a third approach involves testing compounds made naturally by microscopic organisms. Candidates include fungi, viruses and molds, such as those that led to penicillin and other antibiotics. Scientists grow the microorganisms in what they call a fermentation broth, one type of organism per broth. Sometimes 100,000 or more broths are tested to see whether any compound made by a microorganism has a desirable effect.

In the search for a new cholesterol drug, scientists found a fungus that inhibited the HMG-CoA reductase enzyme in a test

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Pharmaceutical firms conduct laboratory and animal research with new drugs before they can begin experiments with humans. Scientists at Hoffmann-La Roche conduct basic research into normal life processes (above) as well as studies targeted to developing specific new drugs. The investigator in the above right photo is studying obesity in laboratory rats, with the ultimate goal of developing medicines to control obesity in humans.
(Photos courtesy of Hoffmann-La Roche Inc., Nutley, N.J.)

tube. Chemists then had to identify which of the fungus' dozens of chemical byproducts was actually inhibiting the enzyme. Once that was done, the chemical's structure was analyzed and improved on to enhance its effects.

To this point, the search for a new drug has been confined to a laboratory test tube. Next, scientists have to test those compounds that have shown at least some desired effects in living animals. "We have to find what the drug is doing on the down side," Kuntzman explains.

ANIMAL TESTING

In animal testing, Kuntzman says, drug companies make every effort to use as few animals as possible and to ensure their humane and proper care. Two or more species are typically tested, since a drug may affect one differently from another. Such tests show whether a potential drug has toxic side effects and what its safety is at different doses. The results "point the way for human testing and, much later, product labeling," Kuntzman says.

So far, research has aimed at discovering what a drug does to the body. Now, it must also find out what the body does to the drug. So, in animal testing, scientists measure how much of a drug is absorbed into the blood, how it is broken down chemically in the body, the toxicity of its breakdown products (metabolites), and how quickly the drug and its metabolites are excreted from the body. Sometimes such tests find a metabolite that is more effective than the drug originally picked for development.

Of particular concern is how much of the drug is absorbed into the blood. "If a drug's active ingredients don't get into the blood," Kuntzman says, "it won't work." Scientists may add other chemicals to the drug to help the body absorb it or, on

the other side, to prevent it from being broken down and excreted too soon. Such changes in the drug's structure mean even more testing.

Absorption rates can cause a host of problems. For example, for a certain drug to be effective, 75 percent of it may need to reach the bloodstream. But absorption rates can vary among individuals from, say, 10 percent to 80 percent. So, the drug must be able to produce the desired effects in those who absorb only 10 percent, but not cause intolerable side effects in people who absorb 80 percent.

"If we can improve the absorption rate we can reduce the variation in what real dosages people would be subject to," Kuntzman says. A more standard absorption rate for all individuals, say around 75 percent to 80 percent, would mean that the dose could be reduced and still have the desired effects.

THE WRONG ROAD

By this time in the testing process, many drugs that had seemed promising have fallen by the wayside. More often than many scientists care to admit, researchers have to just give up when a drug is poorly absorbed, is unsafe, or simply doesn't work. "In research you have to know when to cut your losses if you are going down a wrong road," says Merck's Clement Stone. And, he adds, there are many more wrong roads than right ones.

Nevertheless, progress may yet be made. Occasionally, Stone says, a stubborn scientist keeps looking and finds a usable compound after others had given up. In other cases, compounds may be put aside because they failed to work on one disease, only to be taken off the shelf years later and found to work on another.

Such was the case was zidovudine (formerly known as azidothymidine, or AZT), the first drug approved for treatment of AIDS (acquired immune deficiency syndrome). The drug was first studied in 1964 as an anti-cancer drug, but it showed little promise. It was not until the 1980s, when desperate searches began for a way to treat victims of the deadly AIDS virus, that scientists at Burroughs Wellcome Co., of Research Triangle Park, N.C., took another look at zidovudine. After it showed very positive results in human testing, it was quickly approved by FDA in March 1987.

Even so, "a minuscule number of drugs we test ever reach testing in man," says Richard Salvador, a Hoffmann-La Roche vice president and director of preclinical development. The Upjohn Company of Kalamazoo, Mich., estimates that of every 2,000 chemicals studied, only 200 show any potential in early tests. Only 20 of those may be tested in people, and only one may be safe and effective enough to reach pharmacy shelves. Other estimates are gloomier—PMA puts it at one in 10,000.

One of the most important new products to gain FDA approval for testing in people is a vaccine to protect against AIDS. In August 1987, FDA approved human studies of such a vaccine developed by MicroGeneSys, Inc., of West Haven, Conn.

THE ROLE OF FDA

The role of FDA in the early stages of drug research is small. The Food, Drug, and Cosmetic Act requires FDA to ensure that the new drugs developed by pharmaceutical companies are safe and effective. It does not give the agency responsibility to develop new drugs itself. So, FDA physicians, scientists and other staff review test results submitted by drug developers. The purpose: to determine whether the drug is safe enough to test in humans and, if so—after all human testing is completed—to decide whether the drug can be sold to the public and what its label should say about directions for use, side effects, warnings, and the like.

FDA first becomes involved when a drug company has completed its testing in animals and is ready to test a drug on humans. (Actually, some animal testing continues after human tests begin to learn whether long-term use of the drug may cause cancer or birth defects. Also, more animal data may be needed if human tests turn up unexpected effects. And new therapeutic uses may be found by continued animal studies.)

Although FDA usually does not tell drug companies what specific laboratory or animal tests to run, the agency does have regulations and guidelines on the kinds of results FDA expects to see in any request to conduct human testing. "We certainly send signals to the drug companies on what they need to do," says Elaine Esber, director of FDA's Office of Biologics Research and Review.

And the drug companies listen to those signals. Both Hoffmann-La Roche's Kuntzman and Merck's Stone say their companies follow and sometimes exceed FDA's guidelines. "We want to optimize our chances of taking a compound from animal to human testing," Stone says.

So drug research is a long, difficult and costly road, certainly. But sometimes the hard work, the scientific sleuthing, and the time and dollars spent pay off. Such was the case in August 1987, when FDA approved—in nine-and-a-half months—the much studied and much anticipated cholesterol-lowering drug mentioned earlier—lovastatin. That approval holds the promise of longer and better lives for millions of Americans with heart disease and substantial sales for Merck, the drug's developer. FDA's evaluation of lovastatin was aided by the care with which Burroughs Wellcome conducted its studies, presented the results, and responded to requests from agency scientists conducting the review, according to Commissioner Frank E. Young, M.D., Ph.D.

But to scientists like Hoffmann-La Roche's Kuntzman, drug research goes even beyond preventing or curing disease or making money. It is also a tool for finding out more about the human body and its basic life processes.

PROGRESS, NOT PERFECTION

"Research is an evolutionary process," Kuntzman says. "You change studies and use experiments to lead to other experiments. As you go along you may not even see the connection between studies. In a sense, research has no end. The only end would be when we understand everything there is to know about the human body. I expect that we will never know enough about the body."

Merck's Eve Slater agrees. "We can make progress," she says, "but we are unlikely to achieve perfection." In the end, that is what researching and developing new drugs is all about—understanding and progress. ■

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Tab 55

LIABILITY

The Legal Revolution and Its Consequences

PETER W. HUBER

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The Innovator Departs

Who fled most quickly for shelter from the baying new tort pack? Those quickest on their feet, of course—the person of action, the company of initiative, the mover, the shaker, and the doer. When it comes to liability problems, the bold innovators are the most fleet-footed of potential defendants. More often than not, they adjusted to the threat of liability by doing less. *Not* innovating is a remarkably easy thing to do.

The Founders had promised quite the opposite—a steady march of innovation and progress impelled by the pursuing avengers of liability. The pursuit was there all right. But the innovation did not follow. To the contrary, in the very markets where the legal pursuit was the most intense—on the trail of exotic drugs, contraceptives, pesticides, small planes and cars, hazardous waste disposal, and medical procedures—the mood among suppliers became most sullen, hostile, defensive, and then coldly stagnant. Soon tired of running, the fox retreated to its burrow and refused to come out.

Research expenditures by U.S. companies working on contraceptives peaked in 1973 and plummeted 90 percent in the next decade. Steroidal oral contraceptives in this country underwent no significant changes after 1976, and no truly new contraceptive chemical entities have been introduced since 1968. Clinical tests of a contraceptive implant system called Capronor, developed by the National Institutes of Health, were stalled for more than a year for lack of liability insurance. The implanted contraceptive Norplant, which releases a hormone for five years, was developed by the New York Population Council and as of 1986 was on the market in five other countries. But no American firm dared to market it at home. A new and effective IUD, the Copper-T 380A, won FDA approval, but no major firm was willing to market it for several years. In late 1987, one tiny company finally announced that it would sell the product, at a price vastly above the cost of manufacture, and without any liability insurance (which was, in any event, unavailable), presumably on the assumption that if a wave of lawsuits struck, bankruptcy would provide a quick and clean exit from the market. So the United States, a leader in contraceptive research and marketing well into the early 1960s, has today lost its edge and its hunger for progress. Research on other aspects of reproduction has suffered as well. "Who in his right mind," the president of a major pharmaceutical company asked in 1986, "would work on a product today that would be used by pregnant women?"

The story has been much the same in other high-tech markets favored with attention from the liability system in recent years. Between 1965 and 1985, the number of U.S. vaccine manufacturers shrank by more than half; by 1986 the nation depended on a single supplier for vaccines against polio, rubella, measles, mumps, and rabies. In the 1960s there were eight U.S. manufacturers of whooping cough vaccine; by 1986 there were only two. And only two major companies, Merck and Lederle Labs, were still investing heavily in vaccine research. America, once the world leader in this technology so vital to the public health, was quickly losing ground here too.

Consulting engineers report that they systematically favor old products over new ones in their design specifications, fearing (quite correctly) that newer design options carry a greater risk of liability, whatever real decrease in risk they might actually represent. Liability-conscious universities decline to license patents to small companies, despite the fertile environment they offer for innovation, fearing that anyone suing over a patent-related product would be sure to go for the university's deep pocket as well. Liability concerns forced a Virginia engineer to abandon his business of designing better hand controls for cars used by the handicapped, a business he had set up after his own son had been crippled in a motorcycle accident.

America, land of the Wright brothers, has lost even its appetite for innovation in small planes. Burt Rutan, the pioneering designer of the *Voyager,* didn't have the resources to compete with larger manufacturers, but he had a cheaper way of getting his products out into the marketplace. He sold construction plans for novel airplanes to do-it-yourselfers, who built the planes in their garages. But in 1985, fearful of the lawsuits that would follow if a home-built plane based on his designs crashed, he stopped selling the plans.

As the new tort soldiers marched forward, in whatever field, technologists fell back; it was that simple. The phenomenon ran so contrary to the accepted articles of the new tort faith that many in the law-and-economics priesthood doggedly refused to acknowledge the facts at all. Their theories had declared, quite emphatically, that sharper liability would spur more innovation. How could the facts dare to be otherwise? The answer was that the accepted theories were wrong.

The theories depended, first of all, on a fine-tuned and highly predictable legal process which consistently disfavored more dangerous products and favored safer ones. The success of the new liability engine thus depended on great precision in the courts. But the legal assembly line relied on unskilled workers, heavily pressed for time and with many extraneous

factors—sympathy for the victim most especially—on their minds. This introduced a great uncertainty into the system. And there are limits to the total uncertainty—scientific plus regulatory—that any endeavor can tolerate. With innovative science and technology, that limit is reached much sooner than with the old and familiar.

Worse still, the new tort theoreticians penned a book of new legal rules that discouraged innovation at every turn. From the innovator's perspective, much of the damage was done at the very beginning, when the courts replaced negligence with strict liability. The negligence standard had inquired whether the technologist—the human actor on the scene—was careful, prudently trained, and properly supervised. Who is most likely to pass a negligence test? The best and the brightest—the technologists working at the leading edge of their professions. It is at the frontiers of science, after all, that the best engineers, pharmacologists, doctors, and chemists typically congregate. Under the new legal standards, however, the people themselves, and their good care, good training, and good faith, were quite irrelevant. The new inquest concerned the product itself and its alleged defects. Where once human conduct had been its focus, the tort system now placed technology itself in the dock.

This seemingly modest change sharply tilted the system against innovation. The reason lies in quite understandable human psychology. Jurors can make reasonably sensible intuitive judgments about people—even about professionals—because we are all in the people-judging business every day of our lives. But jurors are not experts about technology itself, and intuition here is a terrible guide. When a juror is asked to categorize technologies—as distinct from their inventors or managers—as good, bad, or ugly, the answers follow a quite predictable pattern. Age, familiarity, and ubiquity are the most powerful legitimizing forces known to the layperson. The inexpert juror is predisposed at every turn to identify technologies that are novel, exotic, unfamiliar, or adventuresome as unwelcome and fraught with danger—in short, defective.

It is a matter of human nature, an instinct as ancient as the species itself. Mothers who stay at home underestimate the familiar risks of their own environment—electric sockets, bottles of cleaning fluid, pediatric services, and cars, while overestimating the less familiar hazards of chemical pollution and nuclear power. Blue-collar workers see too little threat in their familiar cigarettes, alcohol, and construction-site environments, and too much threat in the less familiar hazards of air travel or high-tech medicine. People everywhere underestimate the risks they know well and face every day and overestimate those that are new and foreign. The familiar is safe,

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Biopsychobehavioral Correlates of Insomnia, V: Clinical Characteristics and Behavioral Correlates

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The authors compared two large samples of insomniac patients with a group of control subjects. Sleep difficulty usually began before the age of 40 and generally persisted for many years (average duration, 14 years). Several characteristic behaviors were correlated with the symptom of insomnia. During the day and at bedtime, patients reported difficulty relaxing and frequently described themselves as tense, anxious, overly preoccupied, worried, and depressed. Reports of poor mental and physical health were far more prevalent in the insomniac patients than in control subjects. These results indicate that psychiatric factors need to be a primary focus in the multidimensional treatment of chronic insomnia.

(Am J Psychiatry 141:1371–1376, 1984)

Insomnia is a prevalent symptom (1–4) of a wide spectrum of psychiatric and medical disorders and situational disturbances (5–11 and *DSM-III*). When longstanding and severe, this symptom profoundly affects patients' lives and often becomes the central focus of distress, obscuring the factors involved in the development of the insomnia.

As a result, when seeking treatment insomniac patients frequently perceive their sleep problem as their primary disorder. To accurately assess the problem and to formulate effective treatment plans, psychiatrists need to elicit specific details concerning the condition's onset, clinical course, and characteristics. To date, however, these factors have received little attention in terms of clinical research.

Our primary goals in this study, therefore, were to assess the onset, clinical characteristics, and behavioral and psychosocial correlates of chronic insomnia. Accordingly, we evaluated two large samples of adult patients with a primary complaint of chronic insomnia. In one group, data on the onset and clinical characteristics of insomnia were gathered through comprehensive sleep histories. In another group, responses to specific items on the MMPI related to sleep, behavioral, health, and psychosocial factors were compared with those of control subjects.

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METHOD

In our Sleep Disorders Clinic we evaluated 100 consecutive patients with a primary complaint of chronic insomnia of at least 1 year's duration. These same patients made up the sample of a previous study in which multiaxial diagnoses were made according to *DSM-III* (11). The insomniac patients were 47 men and 53 women between the ages of 18 and 84 years (mean±SE age, 47.9±1.6 years). Seventeen percent were less than 30 years old, 34% were between 30 and 49 years old, and 49% were 50 years old or older. Each patient completed at home a comprehensive questionnaire consisting of more than 350 coded items that provided detailed demographic information, a sleep history, physical and mental health profiles, and a description of current and past use of medication, alcohol, tobacco, and caffeine.

The same questionnaire was completed by a sample of 100 control subjects, consisting of 41 men and 59 women (mean±SE age, 48.2±1.5 years; range, 24–80 years) who were screened to ensure that they were without a sleep complaint or severe medical illness, not using any medication, and able to comply with the study requirements. These subjects were recruited from volunteers in the community, medical and technical staff and students of the medical center, and their friends and acquaintances, all of whom responded to advertisements for good sleepers. As previously reported (11, 12), none of the patients or control subjects was found to have sleep apnea or nocturnal myoclonus as a clinical condition. There were no significant differences between insomniac patients and control subjects in terms of socioeconomic status, educational level, marital status, or general living arrangements.

We have reported previously on the MMPI patterns of patients with chronic insomnia (13, 14). This study focuses on responses to individual MMPI items relat-

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PSYCHIATRIC MEDICINE

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Editor in Chief

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Sleep Disorders in Psychiatric Practice

Richard M. Berlin, M.D. and Constantin R. Soldatos, M.D.
Guest Editors

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Psychiatric Medicine—Vol. 4, No. 2

Treatment of Sleep Disorders

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Sleep disorders are quite common in the general population and frequently encountered in medical practice. In a survey of the adult population of a large metropolitan area (Los Angeles), more than half (52.1%) reported a current or previous sleep disorder.[1] Specifically, the prevalence for various sleep disorders, either currently or in the past, was: insomnia, 42.5%; nightmares, 11.2%; some type of excessive daytime sleepiness, 7.1%; and sleepwalking, 2.5%.

Physicians in a nationwide survey[2] reported that an average of 17% of their patients had insomnia; psychiatrists reported the highest prevalence of insomnia, 32%. For other sleep disorders the estimated prevalence was as follows: nightmares, 4.3%; hypersomnia, 2.9%; enuresis, 2.2%; night terrors, 1.2%; somnambulism, 0.6%; and narcolepsy, 0.6%. Psychiatrists and child psychiatrists most frequently reported patients with insomnia, nightmares, and hypersomnia, whereas child psychiatrists and pediatricians more often encountered enuresis, somnambulism, and night terrors.[2] Thus, in psychiatric practice the evaluation and treatment of sleep disorders constitutes an important area.[3-6] Most often both evaluation and treatment of the patient with a sleep disorder can be accomplished in the office setting.[7]

Emotional factors are predominant in the etiology of insomnia,[3,5,8-10] some types of hypersomnia[6,11,12] and secondary enuresis,[5,13] and in adult sleepwalking,[5,14] night terrors,[5,15] and nightmares.[5,16] However, childhood sleepwalking,[5,14,17] night terrors,[5,15] nightmares,[5,18] and primary enuresis[5,19,20] are most often related to maturational factors. Sleep disorders such as nar-

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colepsy[6,21-25] and sleep apnea[6,26-29] are caused by organic factors (either obvious or presumed) but often have extensive psychosocial consequences, which frequently cause secondary psychopathology.[6,24,25,29]

Using the sleep history, psychiatric assessment, general medical assessment and drug history, the psychiatrist is in the best position to comprehensively evaluate and treat sleep disorders with either primary or secondary psychopathology.[5-7] With the exception of sleep apnea patients who must be evaluated in the sleep laboratory, evaluation and treatment are completed in the office setting.[3-7]

There have been problems with the diagnostic classification of sleep disorders. An unofficial classification, which appeared as an appendix in DSM-III, presented with many serious shortcomings including: excessive number of diagnoses (about 70); many unsubstantiated and confusing diagnostic terms with little validity; over-reliance on expensive sleep laboratory tests; neglect of psychobehavioral dimensions of sleep disorders; and incompatibility with a multiaxial format. A number of these problems have been recognized and resolved in the DSM-III-R. In this classification only a dozen specific sleep disorders are grouped into: dyssomnias (insomnias, hypersomnias and sleep-wake schedule disorders) with the predominant disturbance in the amount, quality or timing of sleep; and parasomnias (sleepwalking, night terrors and nightmares) where abnormal episodic events occur during sleep. Because this classification relies on physicians' clinical skill rather than an unnecessary focus on sleep laboratory procedures, it facilitates management of sleep disorders by the physician in the office setting.

In this chapter we summarize data from recent studies regarding the nature of psychopathology in insomnia,[5,8-10] sleepwalking,[5,14] night terrors,[5,15] and nightmares,[5,16] as well as the psychological correlates and psychosocial consequences of narcolepsy[6,24] and sleep apnea.[6,29] We also present recommendations for the management of these disorders.[3-6]

INSOMNIA

Clinical Characteristics

Insomnia is a symptom of various medical, psychiatric, pharmacologic, and situational conditions. At times, however, particularly when insomnia is chronic and severe, it may affect the patient's life so much that the patient considers it as a distinct disorder in itself.[3,5] Difficulty falling asleep is the most frequent problem, either as a single complaint or in combination with difficulty staying asleep or early final awakening.[5,30] (See following table.)

Clinical Features of Insomnia, Narcolepsy, and Sleep Apnea

Insomnia
- Complaint of difficulty in falling asleep, staying asleep, or awakening too early
- More common in women and the elderly
- Relatively high levels of psychopathology often present
- Patterns of depression, anxiety, and obsessive/compulsiveness are common
- Irregular schedules and activity levels or napping may be factors, especially in elderly patients
- Medical illness or drug use should be excluded as causes

Narcolepsy
- Excessive daytime sleepiness characteristic at onset
- Onset often in childhood or adolescence, but diagnosis delayed
- Sleep attacks of short duration
- Auxiliary symptoms of cataplexy, hypnagogic hallucinations, or sleep paralysis most often present
- If cataplexy is present, diagnosis is confirmed
- Often a family history of disorders of excessive sleep
- Psychopathology is secondary to psychosocial consequences of the condition

Sleep Apnea
- Gasping and choking and/or periodic loud snorting sounds with intervals of breath cessation of more than 10 seconds
- Often associated with excessive daytime sleepiness
- Excessive thrashing movements during sleep
- Morning headaches often reported

Modified from Kales et al[7]

Insomnia is more prevalent with increasing age, in women, in association with psychological disturbances, and among individuals of lower educational and socioeconomic status.[1,5,31-35] Insomniac patients generally tend to overestimate the various measures of their sleep difficulty.[36-38] Nevertheless, sleep laboratory studies have shown that they do have significantly more sleep difficulty than normal sleepers, and discriminant function analysis based on sleep measures, personality variables, or both has successfully differentiated insomniacs from normal controls.[39-42] Thus, the complaint of insomnia should generally be considered as valid by the clinician.

Insomnia may be transient (occurring in response to various stressful events, medical conditions, or pharmacologic agents), or chronic (more or less ingrained into the patient's life style.)[3-5] Patients with chronic insomnia manifest typical behaviors during the day and prior to sleep.[30] During the day they characteristically feel depressed, worried, tense, irritable, and preoccupied with themselves.[30] Not surprisingly, at bedtime they report that they have difficulty relaxing; they describe themselves as feeling tense, anxious, worried, or depressed, and as though their "minds are racing."

Tab 58

Evaluation and Treatment of Insomnia

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excessive sleep: men and women who reported sleeping ten hours or more had about 1.8 times the mortality rate of those who reported 7.0 to 7.9 hours of sleep. In the same study, those who often used sleeping pills had 1.5 times the mortality rate of those who never had used sleep medication. Overall, the data supported the common notion that the asymptomatic or healthy person sleeps about eight hours a night. The authors point out, however, that their data need to be interpreted conservatively because they were not able to control for all major illnesses.[40]

Although this information on optimum sleep length may be useful in understanding the role of sleep in general health status, the clinician needs to keep in mind that the need for sleep varies widely from person to person. An additional problem in quantitatively assessing sleep needs arises with insomniacs, who frequently overestimate their sleep difficulty[45-51] (see also Chapter 3, Sleep Laboratory Studies of Insomnia).

Psychosocial Correlates of Insomnia

Insomnia as a Chronic Psychobehavioral Disorder

More than 30 million people in the United States are disabled by chronic conditions, and half of them are considered to have major disabilities.[52] Among these disabling conditions are psychobehavioral disorders (such as chronic pain syndromes and obesity), which, although functional in nature, are characterized by excessive somatic symptomatology.[53] We believe that chronic insomnia should be included in this category. Unlike chronic medical illnesses that have distinct organic pathology, such as arthritis, diabetes, and emphysema, chronic psychobehavioral disorders usually lack any demonstrable pathology, or, if pathology is present, the symptoms are grossly disproportionate to it.

The treatment of chronic psychobehavioral disorders such as insomnia is a major challenge to modern medicine. These conditions are usually refractory to conventional medical treatment and have a major economic impact. Conservatively estimated, the cost of chronic disabling conditions in the United States, in general, is well over $100 billion annually.[52] The cost of one psychobehavioral disorder alone, chronic pain, was estimated to be between $35 and $50 billion in 1976.[54] Similarly, one of the most costly consequences of chronic insomnia may be its economic impact on the public.

difficulty falling asleep,[3,7,8] as well as reporting lighter sleep with more frequent awakenings.[7,11] An increased prevalence of insomnia has also been associated with psychologic disturbances[3,5,7,12,13,14] and lower socioeconomic status.[3,6,7,10,15] These two factors that increase the likelihood of insomniac complaints appear to be related, because mental health disorders are more prevalent among persons of lower socioeconomic status[16,17] and social class has been found to be inversely related to degree of life stress, as measured by life-change events.[18] Furthermore, the noise, crowding, and other conditions associated with disadvantaged social environments may also contribute to sleep disturbance.[19]

Two nationwide health surveys in the United States have shown that insomnia is experienced by a considerable proportion of the general population; one revealed a prevalence of 21 percent,[4] and the other, 32 percent.[9] Regional surveys have produced similar percentages. In the Los Angeles metropolitan area, the estimated prevalence of insomnia was 32 percent,[3] while a survey in Alachua County, Florida, showed a prevalence of 35 percent.[6] The slight variations in prevalence among these four large surveys were probably caused by differences in the questions asked. Specifically, the three surveys in closest agreement (32%, 32%, and 35%) asked about "difficulty sleeping at least sometimes,"[3,6,9] whereas the study reporting the lowest figure for sleep difficulty (21%) asked specifically about insomnia.[4]

In one of the U.S. nationwide surveys, insomnia was reported more frequently by older subjects and was more common among women (26%) than men (13%).[4] In the other U.S. health survey, which included more than 6,000 adults, difficulty falling asleep or staying asleep was a problem "at least sometimes" for 40 percent of the women and for 30 percent of the men. Sleep difficulties were more common among older subjects, especially women.[9]

In the Los Angeles metropolitan area survey, insomnia was more common among older individuals, particularly women, and among persons of lower educational and socioeconomic status.[3] It was also correlated with more frequent mental health difficulties and physical problems. The prevalence of current complaints of difficulty sleeping was 32 percent, while the prevalence of such complaints at any time during the respondents' lives was 42 percent.

Consistent with the other surveys, the Alachua County study showed that trouble sleeping was more prevalent among older people.[6] Also, hypnotic drugs were used more often by older subjects, particularly

Table 2.1. Prevalence of Insomnia

Area Represented in Survey	*Sample Size*	*Prevalence of Difficulty Sleeping*	*Factors Affecting Prevalence**
United States[4]	1,064,004	21%	A, S
United States[9]	6,672	32%	A, S
Alachua County, Florida[6]	1,645	35%	A, S, SES
Los Angeles, California[3]	1,006	32%	A, S, SES

* A = Age; S = Sex; SES = Socioeconomic Status

by women and by divorced, widowed, or separated individuals. Among the 35 percent of respondents who had difficulty sleeping, the following categories of frequency were reported: 22 percent had difficulty sleeping "sometimes" and 13 percent, "often" or "all of the time."

Table 2.1 summarizes data on the prevalence of insomnia from the two nationwide surveys and two regional surveys conducted in the United States.

Two other surveys of note were conducted in the United Kingdom.[7,8] An assessment of over 2,000 adults in the cities of Dundee and Glasgow, Scotland, showed that sleep difficulty increased with age.[7] Reports of nervousness were also related to sleep difficulty; those who described themselves as being nervous reported more difficulty getting to sleep and staying asleep. This study also indicated that sleep difficulty was more prevalent among the less advantaged social classes. Finally, it showed that when compared with men, women reported that their sleep difficulty began at an earlier age and presented with more complaints of sleep disturbance, a higher incidence of nervousness, and more frequent use of hypnotic drugs. In a study conducted in Merseyside, England, the frequency of both nocturnal sleep disturbance and daytime naps increased with age.[8]

Because of its high prevalence in the general population, insomnia is understandably the sleep disturbance encountered most frequently by physicians. A nationwide survey of physicians indicated that 19 percent of all adult medical patients (aged 18 and older) complain of insomnia.[2] When medical specialties in this survey were compared, psychiatric patients had the highest percentage (35%) of complaints of insomnia. The frequency of complaints of insomnia for adult patients in other specialties was as follows: surgery, 22%; internal medicine, 18%; family–general practice, 16%; neurology, 16%; and obstetrics–gynecology,

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Food and Drug Administration's Adverse Drug Reaction Monitoring Program

Beulah Lee and Wayne M. Turner

The adverse drug reaction monitoring program of the Division of Drug Experience within the FDA is described.

Historical information on the development and activities of the current drug reaction monitoring program, and goals and objectives of the current program are discussed. Also presented are a brief description of the Voluntary Reporting System, intensive drug monitoring studies and special epidemiologic studies, and a workable definition of alert reports and examples of their previous role within the FDA.

Pharmacists should participate actively in adverse drug reaction monitoring.

Key words: Drugs, adverse reactions; Food and Drug Administration (U.S.); Methodology

In 1952, reports of an association between chloramphenicol and aplastic anemia were appearing in the literature. Among the first reports written were two by well-known American hematologists, Wintrobe[1] and Sturgeon.[2] Further inquiries within the medical community provided additional confirmation of this new, rare and serious suspected drug effect. This event led to the awareness of a lack in effective monitoring for adverse drug reactions once a drug has been approved and marketed. Thus, the Committee on Blood Dyscrasias was established in 1954 under the guidance of the AMA for the development of a Registry on Blood Dyscrasias. In 1961, an increasing awareness of drug reactions resulted in the expansion of this committee into the Committee on Adverse Reactions, and the Registry began to monitor all adverse drug reactions (ADRs). During that same year, the FDA also created an adverse drug effects reporting system. It was agreed that FDA would focus on collecting data from universities, government and teaching hospitals, while the AMA Registry would concentrate on data from individual physicians and smaller hospitals. There was to be a free exchange of information.[3] As a result of under-reporting, lack of information provided, inability to determine incidence rates and the parallel efforts of the FDA, the AMA's Registry of Adverse Reactions was discontinued in 1970.[3,4]

In 1970, as a result of a reorganization of the Bureau of Drugs, the adverse drug reaction monitoring functions were delegated to the Division of Drug Experience (DDE). DDE was established to:

1. Collect and evaluate information on drug usage, adverse reactions and other drug experience data,
2. Disseminate drug information throughout the Bureau and other organizations,
3. Evaluate the socioeconomic implications of drug use information,
4. Participate in the World Health Organization (WHO) drug monitoring program,
5. Promote drug epidemiologic and drug monitoring research, and
6. Conduct studies obtaining drug-use trends.

FDA's complex objectives for monitoring ADRs were better recognized in the ensuing years. There were vital needs for: (1) monitoring acute adverse effects of newly-marketed drugs, (2) generating and capturing well-documented spontaneous reports, (3) detecting rare and long-term drug effects, (4) surveying drug morbidity and mortality, (5) developing a national adverse drug reaction information center, and (6) disseminating evaluated drug use and drug reaction data.

Currently, DDE uses five sources to meet the majority of its needs for monitoring adverse drug effects. These are:

1. A Voluntary Reporting System, consisting of spontaneous reports, manufacturers' (mandatory) reports and special registry reports,

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2. Intensive drug monitoring studies,
3. Special epidemiologic studies,
4. Communications with WHO and national drug monitoring centers, and
5. Published literature.

To expand upon these sources, an experiment in postmarketing surveillance is underway, cosponsored by the National Bureau of Standards (NBS), FDA and the Joint Commission on Prescription Drug Use (JCPDU). This effort is directed at "identifying and analyzing the legal policy, and technical implications and consequences of postmarketing surveillance of new drugs, and designing and testing one or more systems to identify or further characterize relatively common, serious adverse effects which can be seen within two years following marketing."[6] The experiment is divided into two phases. At the end of Phase I, several proposed designs including their implementation and methodology for evaluating effects and costs of postmarketing surveillance systems, would be available to FDA, NBS and JCPDU. Phase II will test and evaluate one or more of the systems developed under Phase I. Projected completion date of this study is late 1980.

Surveillance Sources

Voluntary Reporting System (also known as Spontaneous Reporting System). (*1*) *Spontaneous Reports.* FDA's spontaneous reports are dependent upon participation by health professionals in private practice or hospital settings. Reports of adverse drug reactions are mailed directly to DDE. Two drug experience report forms have already been sent to community practitioners. The original long form (FD-1639) is preferred because it contains approximately 25 data elements and, if properly completed, should provide case reports that may be evaluated thoroughly. This form has been used successfully in hospitals. However, because of its length, it is rarely used by private practitioners. Thus, a short form (FD-1639a) was developed which had the benefit of brevity (13 versus 25 data elements) and the convenience of a self-addressed, prestamped format. This form is periodically attached to the *FDA Drug Bulletin* which is sent to over one million health care professionals. Widespread distribution of this latter form to community practitioners has resulted in increased participation in the program.[6]

(*2*) *Manufacturer (Mandatory) Reports.* In late 1962, the Food, Drug and Cosmetic Act was revised under the Kefauver-Harris Amendments to require manufacturers with an approved New Drug Application (NDA) to report adverse drug reactions to FDA. These reports, collected voluntarily from health professionals, are submitted to FDA on a regular basis.

(*3*) *Special Registry Reports.* Special registries collect and evaluate the occurrence and recurrence of adverse drug reactions and their most frequent patterns or sequences. They are responsible for consolidating prior and current data on adverse effects.

An example of a specialty registry is the Armed Forces Institute of Pathology's Registry of Tissue Reactions to Drugs which correlates morphologic biopsy and necropsy data with the historical, clinical, medicinal and laboratory data of the patient.[7] Clinicopathologic studies of cases which have in common a particular organ or category of reactions to a particular type of drug are published periodically (e.g., liver reactions to oral contraceptives). These studies may lead to an investigation of the tumorigenic and teratogenic effects of drugs as well as the mechanisms of drug-induced reactions in tissues and cells. Individual cases are submitted voluntarily by the medical community.

The idea of monitoring drug experiences through registries is relatively new to FDA. Existing and past registries have been developed and implemented by professionals with interest in collecting specific types of data. FDA has financially supported some of these efforts, (e.g., contrast agents, ocular side effects). In the interest of monitoring drug safety and efficacy, a future goal of the FDA is to stimulate and support new registries of adverse drug experiences.

The major benefits of the Voluntary Reporting System include the infinite size of the reporting sources, the availability for active involvement by health professionals and the relatively inexpensive cost of materials. In addition, its ability to support known reactions and to uncover rare, serious or fatal reactions allows for the generation of hypotheses for further studies. Major criticisms of the system include gross under-reporting, difficulty in obtaining follow-up information and the inability to derive incidence rates (lack of denominator data).

Intensive Drug Monitoring Studies. Intensive drug monitoring studies (e.g., Boston Collaborative Drug Surveillance Program) provide systematic and detailed collection of data from well-defined groups of inpatients. The surveillance is done by specially trained health professionals (e.g., nurse monitors, clinical pharmacists) who devote their full-time efforts toward recording all drugs administered and all events which might conceivably be drug-induced.[8] Subsequently, statistical screening for drug-event associations may lead to special studies.

The major benefits of these studies include the ability to: (1) derive incidence rates, (2) analyze factors which may contribute to reactions, (3) identify drug interactions and study them, (4) detect previously unrecognized reactions, and (5) generate and test hypotheses. Criticisms have included: (1) the great expense of resources, (2) the relatively small population size resulting in nonidentification of rare reactions, (3) the relatively short period of observation resulting in nonidentification of delayed reactions, and (4) the lack of follow-up and outcome information. Ongoing studies include the acute medical, surgical and pediatric care settings which limit the drug monitoring only to those drugs which are characteristic of medical, surgical and pediatric inpatient use.

Special Epidemiologic Studies. Special epidemiologic studies (e.g., Drug Epidemiology Unit, Boston University Medical Center[9]) detect associations between major disease outcomes and drugs used in long-term therapy for outpatients. Case-control and cohort approaches are currently used.

Cohort studies assess the relationship of one or more variables (e.g., drugs) toward increasing the risk of disease development. These variables are measured initially in a group of healthy persons and then are reviewed over a period of time to determine if a particular disease has developed. Some of the major advantages of this type of study are the ability to:

1. Repeat initial measurements of variables,
2. Demonstrate time relationships between the presence of variables and the subsequent disease,
3. Determine incidence,
4. Use the depth and variety of information for several measures of safety (as well as efficacy),
5. Study the effects of known familial and demographic variables,
6. Make follow-up information complete and comprehensive,
7. Generate hypotheses and test them, and
8. Test hypotheses derived elsewhere.

Information bias, loss of follow-up because of attrition, high cost and long-term commitment of funds and personnel, and lack of randomization (versus controlled clinical trials) are some criticisms of cohort studies.

Case-control studies measure the relationship of existing disease states to drugs and other variables. For every group of patients with a particular disease state, a suitable disease-free control group is used for comparison. These studies aim at determining factors (e.g., drugs) responsible for disease development. Some of the advantages of case-control studies include the ability to:

1. Derive relative risks attributable to various factors, including drugs,
2. Detect delayed and rare drug reactions,
3. Identify previously unrecognized reactions,
4. Confirm recognized reactions,
5. Focus on known sources of cases (e.g., specialty and death registries, hospitalized serious cases, even existing cohort studies),
6. Generate hypotheses and test them,
7. Test hypotheses produced by other studies, and
8. Succeed with minimum resources.

Criticisms of this type of study concern the difficulties in selecting appropriate control groups and in collecting comparable information on cases and controls.

Other Sources. To supplement all the previously discussed sources, medical and pharmacy journals are screened each month by DDE personnel to detect new, rare and serious adverse drug reactions published in letters-to-the-editor or in journal articles.[10]

Another means of obtaining additional information is through exchanges with other countries. DDE has been designated by WHO as the National Drug Monitoring Center for the United States. Information is usually acquired from WHO or other national centers through news bulletins, personal communications or international meetings.

Alert Reports

Alert drug reactions are defined by DDE to include:

1. New and unexpected reactions not listed in the labeling,
2. Serious, life-threatening or fatal reactions,
3. Unusual increases in numbers or severity of reactions (clusters),
4. Potential association with congenital anomalies, or
5. Incidents of therapeutic failure which suggest problems with drug bioavailability.

Within DDE, all incoming voluntary reports are immediately screened for alert reactions. These reports are then presented to an Alert Committee meeting which is composed of physicians and pharmacists. The tasks of this committee are to determine whether or not (1) a probability of a causal relationship may be surmised from the suspected reaction(s) to the suspected drug(s), (2) the particular "alert" should be forwarded to FDA's New Drug Evaluation (NDE) Division which has the responsibility of reviewing and evaluating drug safety and efficacy, and (3) follow-up information should be requested and, if so, what additional information is needed for optimal evaluation. Therefore, before FDA issues new proposed labeling changes or drug alerts to the public, consultations have occurred between NDE, expert outside advisors and DDE.

Until recently, because of the difficulties in establishing direct cause and effect relationships between the drug(s) and reaction(s), the Voluntary Reporting System had contributed only indirectly to regulatory action by FDA. It had, however, played a role in helping FDA substantiate and document actual instances of previously unusual and rare adverse reactions that appeared in the literature. Some examples of these are clindamycin and severe lower bowel effects,[11] diethylstilbestrol and vaginal adenocarcinoma in the offspring,[12] sustained-release potassium chloride tablets and severe gastrointestinal ulceration,[13] and ibuprofen and ocular effects.

A significant advance did occur late in 1976 through spontaneous reports which involved direct initiation of regulatory action. Several reports associating gamma benzene hexachloride with central nervous system (CNS) toxicity were received.[14,15] Although prior to this time it was known that variable percutaneous absorption could occur from its topical application in humans, the resulting CNS toxicity was not well established. These reports provided the necessary clinical support which contributed to new warnings in the official labeling.[16]

History also shows that FDA made some premature alert decisions to the public from insufficient evidence. These may have led to injurious delays in drug testing and drug usage. Two examples are: (1) dimethylsulfoxide (DMSO) and lens clouding, which was later concluded to occur only in animals,[17] and (2) the original multifilament Dalkon shield and septic abortions or maternal deaths, which was later concluded by FDA to differ insignificantly from other IUDs.[18,19]

As can be seen, there is a problem of identifying and evaluating previously unknown drug reactions. At times, FDA is suffering from drug information gaps and the difficult choice of quantifying the benefits as well as the risks of certain drugs. However, health professionals and the public

must understand that the success and failure of ADR alerts is dependent upon astute suspicions that an unnecessary risk is being taken by the patient. Often, these observations or information gaps can be provided by any member of the health care team.

Summary and Conclusion

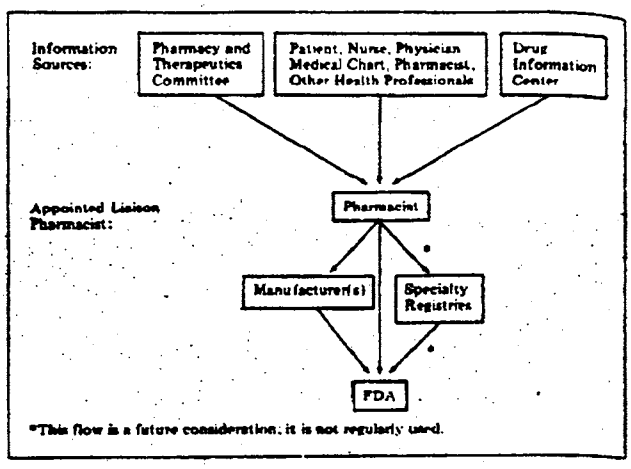
FDA uses five surveillance sources to monitor adverse drug reactions. The primary focus of the program is collecting new, rare and unpublished suspected drug effects. A major surveillance source depends upon information and materials received voluntarily from health professionals.

Pharmacists are in a unique position to use their proximity and frequent communications with medical personnel to obtain ADR information. They have access to suspected alert reactions from their oral exchanges with staff physicians, nurses, students and fellow pharmacists. FDA's experience has been that adverse drug reaction reporting is unrewarding and time-consuming for the physician. This provides a great opportunity for pharmacists to participate in a professional service which contributes toward drug safety.

A successful methodology used in private practice and in hospital settings for participating in the Voluntary Reporting System involves the collection of data by a single pharmacist. This person should be motivated to accept the responsibilities of collecting the information needed in the suspected drug-reaction association, discussing the information with an appointed committee or other fellow consultants, sending the information to DDE and following through on additional information if requested (Figure 1).

It is well recognized that greater pharmacist involvement in health care is needed. The identification of new, rare or unusual adverse drug reactions enables the FDA to reassess whether or not the benefits of a drug outweigh the risks. Cooperation by all pharmacists and other health professionals is vital for the success of a voluntary program.

Figure 1. Suggested procedure for the pharmacist to use when reporting a drug reaction



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PREVENTION BY CHOLINE OF THE DEPLETION OF MEMBRANE PHOSPHATIDYLCHOLINE BY A CHOLINESTERASE INHIBITOR

To the Editor: Choline serves, within cholinergic neurons, as a precursor to both acetylcholine and such membrane phospholipids as phosphatidylcholine.[1] The availability of extracellular choline, provided by the circulation or formed intrasynaptically through acetylcholinesterase-mediated hydrolysis of acetylcholine, can influence the synthesis[1] and release[2] of acetylcholine, the synthesis of phosphatidylcholine,[3] and levels of phosphatidylcholine in membranes.[4] Moreover, the choline in membrane phosphatidylcholine can be mobilized to serve as a precursor to acetylcholine,[5] when extracellular choline is inadequate.[2]

We previously proposed[6] that patients with Alzheimer's disease be given supplemental choline when treated with drugs, such as acetylcholinesterase inhibitors, that diminish the availability of extracellular choline to cholinergic neurons. In such circumstances, the supplemental choline may both enhance the release of acetylcholine[2] and protect the neuron from the depletion of its membrane phospholipids. We now show that, without such supplemental choline, acetylcholinesterase inhibitors can in fact cause the depletion of phospholipids.

Sections of striatum from rats, superfused in Krebs–bicarbonate medium, were stimulated electrically for one to eight periods of 20 minutes each that were separated by similar intervals; the mediums were assayed for acetylcholine, and the tissues for membrane phosphatides. When the acetylcholinesterase inhibitor physostigmine was present in the medium, membrane levels of phosphatidylcholine declined to 76±4 percent of initial values (n = 14). (The levels of the other principal phosphatides also declined stoichiometrically, suggesting that the choline deficiency diminished the amount of membrane in the cell, rather than altered its composition.) Sections stimulated without physostigmine showed no decline in membrane phospholipids (97±4 percent of initial values; n = 7). Moreover, the addition of choline (0.01 to 0.04 mM) to the physostigmine-containing medium caused a dose-dependent enhancement of acetylcholine release and fully protected the sections from phospholipid depletion (103±2 percent of initial values; n = 17).

A multicenter study is about to begin that attempts to confirm earlier studies[7] demonstrating a therapeutic effect of tetrahydroaminoacridine, another acetylcholinesterase inhibitor, in patients with Alzheimer's disease. Although the patients in that earlier trial also received supplemental choline (as lecithin[7]), the announced protocol for the replication study provides only tetrahydroaminoacridine. Our data suggest that failing to give a source of choline to patients receiving acetylcholinesterase inhibitors may decrease phospholipid levels in their cholinergic neurons. Although our data have been derived from in vitro studies, it should be noted that other reports have described elevations in the levels of phospholipid breakdown products within the brains of untreated patients with Alzheimer's disease; such subjects may be especially vulnerable to the depletion of phospholipids caused by acetylcholinesterase inhibition.[8,9]

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Richard J. Wurtman, M.D.
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1. Blusztajn JK, Wurtman RJ. Choline and cholinergic neurons. Science 1983; 221:614-20.
2. Maire J-CE, Wurtman RJ. Effects of electrical stimulation and choline availability on the release and contents of acetylcholine and choline in superfused slices from rat striatum. J Physiol (Paris) 1985; 80:189-95.
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LIABILITY FOR VACCINE-RELATED INJURIES

To the Editor: Japanese encephalitis is a mosquito-borne viral infection that occurs in epidemic and endemic forms in much of Asia.[1] Although infection can be asymptomatic, clinical cases are usually severe and often fatal.

Several vaccines are produced commercially for immunization against this disease. The vaccine produced by BIKEN Corporation in Japan is safe and effective and was approved as an investigational new drug by the Food and Drug Administration.[1] The Centers for Disease Control (CDC) distributed this vaccine to physicians who registered as collaborative investigators. These physicians could then give the vaccine to travelers who would be at risk, using an informed-consent protocol and reporting any adverse effects to the CDC.

On June 30, 1987, the CDC informed the collaborating investigators that the vaccine could no longer be obtained from BIKEN because the company did not have appropriate liability insurance, and there was no statutory mechanism for absolving them of liability. Because of the limited demand, it is unlikely that any American company would undertake the manufacture or distribution of this vaccine.

An increasing number of American companies are seeking business and development opportunities in the Far East. There is also a steady stream of tourists going to areas in which the disease is endemic in India, China, Korea, Nepal, Burma, and Thailand. This number will increase dramatically in 1988, when the Summer Olympics are held in Seoul, South Korea. It is regrettable that these travelers will have to be at risk for a potentially fatal but preventable disease because of a liability issue.

It is apparent that the American public, and not just physicians, are paying a price for the medical malpractice–liability crisis. The Japanese encephalitis vaccine issue is one small but important part of this problem. One way to resolve this particular problem would be to include all vaccines in the no-fault compensation program for childhood vaccinations recently signed into law (and discussed by Iglehart in the May 14 issue[2]). It would also be helpful if such programs were funded; that they were not was a distinct deficiency of the pediatric-oriented legislation at the time of its passage. Good intentions are not enough.

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1. Japanese encephalitis: report of a World Health Organization Working Group. MMWR 1987; 33:119-20, 125.
2. Iglehart JK. Compensating children with vaccine-related injuries. N Engl J Med 1987; 316:1283-8.

The above letter was referred to Mr. Iglehart, who offers the following reply:

To the Editor: Dr. Marcus' letter raises several points about the Vaccine Injury Compensation Act that deserve reaction. It also contains a bit of misinformation that may needlessly alarm some

readers. Dealing with the latter point first, I am informed by the CDC that people who travel to Seoul for the Summer Olympics are considered by the agency to be at negligible risk of contracting Japanese encephalitis. Only if they intend to travel to rural areas of Korea (or of other countries in which the disease is endemic as well) should they possibly be considered candidates for Japanese encephalitis vaccine, according to the CDC.

There appear to be two major reasons why Japanese encephalitis vaccine is not covered by the Vaccine Injury Compensation Program. The first is that it is not a licensed product. The second is that the program was intended to provide compensation for those injured by vaccines required for school entry. One can only speculate about whether the inclusion of Japanese encephalitis vaccine under the program would provide sufficient relief from liability to persuade the manufacturer to seek licensure. One major vaccine manufacturer (Lederle Laboratories) has testified that the program as established under the new law will not reduce its liability.

To date, no funding mechanism has been established for the compensation program, so it has not yet become operational. The House-passed Omnibus Budget Reconciliation Act of 1987 contains provisions that would establish an excise tax to fund future claims and authorize appropriations from general revenues to fund preexisting claims. The excise tax would be $4.56 per dose for diphtheria, tetanus, and pertussis vaccine; $4.44 per dose for measles, mumps, and rubella vaccine; $0.29 per dose for poliomyelitis vaccine (both oral and injectable); and $0.06 per dose for diphtheria and tetanus vaccines. Appropriations to cover preexisting claims would be authorized at a level of $80 million per year for four years. The excise tax would take effect January 1, 1988, but claims could not be filed until October 1, 1988. Other proposed amendments would extend protection to the person who administered a vaccine (a step strongly advocated by physicians' groups), clarify the definition of a compensable condition to include only conditions having a serious impact six months after immunization, and modify benefits for preexisting conditions. The system would have a five-year life, but would be automatically terminated if more than 150 new claims were awarded in any 12-month period. The program strikes balances all along the way, but without such compromises it would never have been created in the first place.

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ACCESS TO HEALTH CARE FOR DISABLED CHILDREN

To the Editor: As chairman of the Committee on Children with Disabilities of the American Academy of Pediatrics, I am writing concerning the Sounding Board article by Butler et al. in the July 16 issue.[1] The analysis deserves considerable praise for effectively describing the difficulties of ensuring access to health care for children with disabilities. However, three issues need further discussion.

First, the authors indicate that there may be discontinuity of coverage as a result of a change in a parent's employment. Our recent Health Care Financing Study of Chronic Illness at Albert Einstein College of Medicine[2] has demonstrated that about 15 percent of families with children who have severe chronic disabilities were denied insurance for either their families or the disabled children. This was often done because of the presence of a "preexisting condition." In addition, some self-insured employers have reportedly denied employment to parents of disabled children because of apparent concern about raising the employer's insurance costs. Health maintenance organizations have also allegedly denied membership to families with disabled children.

Second, as the authors mention, state variations in coverage make it difficult to use Medicaid as a national program to ensure comprehensive health care services for disabled children. Unfortunately, the income-eligibility standards for Medicaid vary from state to state, as does each state's willingness to provide optional services, including many therapies that physically handicapped children require. It would be unwise to force families to become medically indigent in order to qualify for Medicaid, only to receive limited services beyond basic health care. Given states' sensitivity about their rights and prerogatives, Medicaid as it is currently structured would appear to be an unlikely source of comprehensive health care for chronically ill and disabled children.

Third, problems of access to health care for people with disabilities do not end in childhood. A frequently heard criticism is that families can obtain pediatric care for their children with disabilities, but that it is enormously difficult to find physicians with the requisite skills or interest who are willing to care for adults with developmental disabilities.

The view of our American Academy of Pediatrics committee is that comprehensive health care, home care, and catastrophic-illness care for the population with disabilities are inexorably linked, and that Medicaid and private insurance will need to be supplemented by catastrophic-illness insurance if we are to ensure the provision of community-based care for the disabled. In addition, efforts to increase access to care must be coupled with the training of professionals to increase their skills in dealing with the disabled and to correct or mitigate the pejorative attitudes that unfortunately remain pervasive among health care professionals.

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1. Butler JA, Rosenbaum S, Palfrey JS. Ensuring access to health care for children with disabilities. N Engl J Med 1987; 317:162-5.
2. American Academy of Pediatrics. Health care financing for the child with catastrophic costs, June 1987.

The above letter was referred to the authors of the article in question, who offer the following reply:

To the Editor: My coauthors and I are grateful for Dr. Cohen's amplification of our remarks. We certainly concur that preexisting-condition clauses, state variations in Medicaid benefits, problems associated with health care access for older adolescents, and problems of physician training and attitude all can constitute serious obstacles to adequate health care access for disabled children and youth.

Our only concern with the letter is that some may read it as a generalized condemnation of Medicaid, which, although far from perfect, remains the largest single source of insurance for low-income children with disabilities. Optional benefits under the program do vary, but now are often fairly generous. In 1985, for example, 36 states covered services by persons other than physicians, 18 covered private-duty nursing, 36 covered physical therapy, 29 covered occupational therapy, 34 covered therapy for speech, hearing, and language disorders, 48 covered prescription drugs, 45 covered prosthetic devices, 35 covered rehabilitative services, 50 covered intermediate care facilities, 33 covered psychiatric services, and 26 covered personal care services.[1] In addition, all states can now pay for case management. In our own research on children with disabilities in five states, we discovered that publicly insured children had much broader coverage than privately insured children, reflected in the fact that Medicaid-eligible parents paid out of pocket for only 5 percent of all health care visits, whereas privately insured parents paid out of pocket for 23 percent of all visits.[2]

Also, Medicaid is improving its standards of care. Twenty-six states have adopted the federal reforms contained in the Omnibus Budget Reconciliation Act of 1986, allowing states to cover pregnant women and infants whose family income exceeds the payment level established by Aid to Families with Dependent Children but is below the federal poverty level. Congress is currently debating two pieces of legislation: one, proposed by Senator Durenberger, would extend Medicaid benefits to any disabled child whose family income is less than 185 percent of the poverty level; the other, proposed by Senator Bradley and Congressman Waxman, would extend Medicaid eligibility to all pregnant women and infants in that income bracket. These efforts, even if imperfect, are likely to advance far sooner and provide far more benefit to low-income children with disabilities than any contemplated reform of the private insurance industry. To the extent that Congress succeeds in restructuring

Tab 61

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incidental factors are gaining importance as FDA's information quality concerns increase.

§13.11 New Drug Applications: The Process

The drug approval process is the archetype of necessary regulation. Drugs cannot be judged safe or unsafe by the average person who picks up a tablet or bottle; and each drug compound is intended to act in the body with some physiological effect. So there is little dispute about the need to have a governmental drug clearance and regulation process. However, once past that point of consensus the regulatory process by which drugs are cleared becomes controversial for its cost, time, expense, and laxity or rigidity, depending on one's political outlook.[1]

Federal drug approval processes seek a body of safety evidence sufficient to predict whether or not the drug will be harmful. Founded on the tragic experience with untested elixir sulfanilamide,[2] the process helps to identify hazards and to screen out risks which are not justified by therapeutic benefits.[3] Because all drugs have some risks, efficacy studies must show that the drug's contribution to patient care will be sufficient to overcome its hazards.[4]

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study methods which should be used by drug sponsors. 47 Fed Reg 46627 (Oct 19, 1982). Speech by Acting Commissioner Novitch to Conference on Generic Drugs (July 15, 1980). *See also FDA Appropriations: Hearings Before the Subcomm on Agriculture and Related Agencies, Senate Appropriations Comm*, 97th Cong 1st Sess (1981) (testimony of Commissioner Hayes)

[1] *See e.g.*, R Merrill & P Hutt, Food and Drug Law Cases and Materials 409-33 (1979); P Termin, Taking Your Medicine (1979); Comment, *The Food and Drug Administration: Law, Science and Politics in the Evaluation and Control of New Drug Technology* 67 Nw U L Rev 858 (1973). "[T]here can be little doubt that it is more difficult and costly to obtain approval of a new drug in this country than in the other . . . . " Merrill, *Can FAD Do Anything Right?* 2 Va Law School Report 19, 20 (1978)

[2] This drug's fatal ingredient, a diethylene glycol solvent, spurred Congress to adopt the 1938 Act's "new drug" testing for safety. *See* §3.04, Ch 13

[3] Many of the safety-related issues come up in animal testing or during Phase I human testing under an IND, at which point the further development of the drug is dropped. The 1962 amendments were spurred by a teratogenic drug, thalidomide, which was distributed in a poorly controlled investigation. *See* §3.07, Ch 13

[4] 21 USC §505 is a balance of risks and benefits, not an absolute barrier to hazardous drugs. For example, an anticancer agent with liver damage as a side effect may be an acceptable risk for cancer patients. The approved process identifies dosages at which adverse effects occur and quantifies the benefit and hazard probabilities so that a factual judgment can be made on approvability

There have been at least three historical phases to FDA's approval since the 1962 Drug Amendments created FDA's modern drug control powers.[5] In each, communication channels between developer and reviewer have been the index of success for drug approvals. Between 1963 and 1976, the process of approval was a scientific debate, the terms of which were developed through extensive paper submissions. This process did not attract much controversy or attention outside of the pharmaceutical community, compared to its later period. FDA paperwork gradually became longer and more detailed until truckloads of papers constituted a formal new drug application filing.[6] The predominant issue in debate was whether the existence of a premarket proof of efficacy had created a delay in relative availability of necessary therapeutic drugs in the United States as compared to other countries without that requirement. The "drug lag" debate attracted more economists and congressmen than virtually any other subject in the field of FDA regulation.[7]

A lawyer-designed procedural reform effort, which was highly skeptical of FDA drug reviewer dialogue with industry scientists, arrived in the late 1970's.[8] This theory held that "pressure" to approve could be avoided by isolating the reviewers. This proceduralist scheme of drug approval interactions emphasized controls, inspections, and oversight. Contact with reviewers by outside researchers who developed drugs was forbidden except under formalized methods of discourse.[9] While it facially served to cut off improper contacts, it produced an adversary atmosphere in which drug developers and reviewers could barely talk beyond "name, rank and serial number," in

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[5] *See* **§13.02** for the development of 21 USC §505 in the 1962 amendments

[6] Actual case reports on each patient constitute the bulk of the NDA. As soon as the approval letter is issued the actual NDA file is retired to a Federal Records Center, so as to leave more room for storage at FDA. "The average application today contains 100,000 pages, filling hundreds of volumes. Applications arrive at FDA, literally, in truck loads." Address by HHS Secretary Schweiker to National Pharmaceutical Council (June 23, 1982)

[7] *See e.g.*, R Merrill & P Hutt, *supra* note 1, at 430-33; S Peltzman, Regulation of Pharmaceutical Innovation (1974); P Temin, Taking Your Medicine (1979); W Wardell & L Lasagna, Regulation and Drug Development (1975). And *see also* GAO Report, "FDA Drug Approval-A Lengthy Process That Delays the Availability of Important New Drugs," HRD-80-64 (May 28, 1980)

[8] HEW Review Panel on New Drug Regulation, Final Report (May 1977)

[9] "Public" participation would occur by additional committee reviews and public disclosures but the questions which inevitably arise in reviews would not be answerable in a dialogue

the words of a top FDA official.[10] In hindsight, it is ironic that the two principal incidents of alleged improper, or illegal, reviewer conduct occurred during this phase of tighter controls on all drug developer contacts with the FDA.[11] Such incidents were rare, but did not mark the earlier or later periods of freer contacts. Legislation to codify the proceduralist reforms was offered and passed the Senate, but failed to draw a consensus for support during its time in the Congress.[12]

The 1981-84 period of reform in the drug approval process emphasizes communications at all levels as the centerpiece of an effort to expedite the drug approval process. Casting aside some of the proceduralist reforms which had failed to win congressional endorsement, this latest phase brings a confident FDA into more open dialogue with its constituency of drug consumers and manufactures.[13]

The procedures for drug approval today fall into essentially four stages. The drug manufacturer discovers a compound or conducts experiments with a known compound, which is tested in appropriate laboratory screening tests and then is examined in animals as a possible pharmacological entity. Private research funding predominates; public funding aids less marketable products and some drugs for exotic therapies,[14] but for the most part FDA drug reviewers deal with private firms sponsoring the new drug.

FDA's approval process beings with an investigational new drug (IND) application, filed 30 days before first human experimentation with the drug, so as to permit FDA an opportunity to examine the proposed testing.[15] The IND process is undergoing modifications

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[10] H Meyer, Director, National Center for Drugs & Biologics, Address to Washington Forum (June 10, 1982)

[11] The indictment of a drug reviewer for receiving gratuities from a drug developer of DMSO and the firing by FDA of a physician and a statistician for accepting gratuities from a marketer of contact lens sterilizing solution occurred as a result of activities in 1977-80. As one result, the individual former reviewers are being sued and the government refused to pay counsel fees, see "FDA Reviewer Liability in IND/NDA Decision," 44 F-D-C Reports (Pink Sheet) TG-6 (July 19, 1982)

[12] See S Rep No 96-321, regarding S 1705, 96th Cong, 1st Sess (1979)

[13] The confidence was seen in testimony by FDA's new leadership, *see e.g., FDA Oversight Hearings Before House Comm on Govt Operations*, 97th Cong, 2d Sess (Aug 3, 1982) (testimony of FDA Commr A Hayes)

[14] Address by HHS Secretary Schweiker to National Pharmaceutical Council (June 23, 1982)

[15] *See* §13.12

which may reduce delays and assure more prompt development of FDA-drug firm communications.[16]

IND regulations resulting from the 1983 proposed rules will be made final and will become part of the operating system of the National Center for Drugs and Biologics, perhaps in 1984 or 1985. FDA is considering several new ideas, not yet even proposed as rules, under which more of the burden will rest with outside review boards at the first level of clinical approval; overall effect of the proposed new IND rules would be more rapid clearances for the earliest, least intrusive human investigations.[17]

Because safety is a paramount consideration at the more intensive, later stages of drug investigations, the clinical "hold," staying the conclusion of the routine 30-day pretesting period, is more readily applied against larger or more risk-related human experiments performed under INDs after the short initial testing phase.[18] Commercial distribution of the IND product is not allowed, but in some cases FDA will grant written permission for the sale of the investigational product.[19]

The second stage of FDA approval of the process begins with meetings preparatory to the filing of the new drug application (NDA).[20] The FDA should meet with the drug firm and examine the IND evidence to identify special problems and additional testing which is needed. When FDA has a research program in mind, it will usually negotiate with the firm at this stage for additional testing. By the time of the pre-NDA meeting, the firm should have completed Phase I basic human studies and Phase II studies in patients for whom the drug will be expected to produce a therapeutic result.[21]

The goals of those phases are distinct. Phase I seeks pharmacologic effects information and early evidence on effectiveness in

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16 Hayes testimony, supra n 13

17 The Investigational New Drug proposed rules are found at 48 Fed Reg 26720 (June 9, 1983). Discussion of the FDA's desire for future use of the outside review boards is detailed in proposed Investigational New Drug (IND) Regulations preamble *id* at 26722.

18 Proposed rules on clinical hold procedures, 21 CFR §312.42 (proposed), formalize the methods now in use for suspending or delaying the use of the drug in humans.

19 Commercial sale is prohibited without written FDA approval. An example likely to be approved is an expensive orphan drug, for which no sustaining market is yet available. Proposed 21 CFR §312.6, 48 Fed Reg 26737 (June 9, 1983)

20 *Id*

21 *See e.g.*, House Comm on Science and Technology, 96th Cong, 2d Sess, The Food and Drug Administration's Process for Approving New Drugs (Serial HHH Comm Print 1980)

20-60 patients. Phase II measures several hundred closely monitored patients for the clinical effectiveness of the drug. Both prepare the product for its real test, the multiple Phase III effectiveness and safety tests which form the basis for risk assessments and label warnings, during which thousands of patients may be exposed.[22]

FDA and the firm have the greatest interest in results from the Phase III clinical studies, which have been designed to elucidate neutral, "blind" research results. This is the point at which drug products do or do not prove effective in double-blind controlled clinical studies. Evidence generated at this point is crucial to approval. Meetings with FDA continue during this phase as preliminary results are reviewed.[23]

These meetings may be frustrating, for the agency employees may be skeptical. But in tactical terms the persuasion must be done at this level, for it is quite risky to file over protest and then sue the agency after rejection.[24] FDA has procedures for internal appeals, and one should always try the internal appeal option if the issue is a pivotal study or otherwise is of crucial importance.[25]

The final phase of the review process leads to formal acceptance of the proposed NDA. Concurrent reviews of the application by several groups within the National Center for Drugs & Biologics each produce a reviewer's recommendation.[26] Internal meetings within FDA generate questions, and meetings with the drug developer pose those questions. An advisory committee to the FDA may review the new product and advise what additional work needs to be done.[27] Advisory commit-

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[22] Proposed 21 CFR §312.21, 48 Fed Reg 26737 (June 9, 1983)

[23] *Id.* There will be more of these meetings to inform sponsors more quickly of the correctable deficiencies. Address by HHS Secretary Schweiker to National Pharmaceutical Council (June 23, 1982)

[24] Filing under protest means the claiming of an opportunity for a hearing. At this point, the application will be denied, the hearing will probably be denied, and the courts will probably defer to FDA's wisdom in reviewing the application. So the procedure will be seldom utilized. 21 CFR §314.110(c) (proposed), 47 Fed Reg 46655 (Oct 19, 1982)

[25] Internal appeals within the Office of New Drug Evaluation are a commonly available internal remedy to appeal disagreements. Preamble to NDA Proposed Rules, 47 Fed Reg 46633-34 (Oct 19, 1982)

[26] Concurrent review allows each reviewer to have a detailed technical section on that person's area of responsibility and a 50- to 200-page summary of the total NDA technical data

[27] Advisory committees review the progress of studies and suggest additional studies. "Sterling's Trilostane . . . Recommended," 44 F-D-C Reports (Pink Sheet) TG-9 (June 28, 1982). Advisory committees were involved in the decision to clear for marketing the anti-inflammatory drug Oraflex in 1982. *FDA Oversight Hearings Before House Comm on Govt Operations*, 97th Cong, 2d Sess (Aug 3, 1982) (testimony of FDA Commr A Hayes)

tee clearance is a helpful step for FDA, but as a legal matter does not represent a required step of approval and does not speed up the process.[28]

After the FDA is satisfied with the product's adequate and well-controlled studies showing its safety and effectiveness, the agency collects other necessary information, as by validation of testing methods.[29] FDA's field force inspects the manufacturing facility for compliance with good manufacturing practices.[30] The verification of inactive ingredient safety may involve review of a master file, submitted directly to FDA as a proprietary protection by the inactive ingredient supplier.[31] Labeling claims receive a preliminary review.[32]

After these reviews, the hierarchy within the FDA drug operation endorses the recommendation to approve the NDA.[33] Time delays at this stage may be significant, for the demise of an approved drug product through adverse patient reactions quite often leads to adverse congressional questioning of the drug approval managers. Managers, because of this disincentive to speed through reviews, may ask questions which delay the process, or may sit on an application until stimulated. In the parallel example of "paper NDAs," discussed as a separate process in a later section,[34] the FDA has delegated approval authority for all paper NDAs after the first one in a product class (i.e.,

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[28] For example, a sponsor whose NDA was delayed in the FDA for years could not persuade a court to order FDA action on the NDA even though the advisory committee had already cleared the product. *Newport Pharmaceuticals Intl Inc v Schweiker*, Food Drug Cos L Rep (CCH) ¶38148 (DC DC 1981)

[29] Methods validation permits an FDA laboratory which analyzes the purity of the drug to duplicate the sponsor's testing method. This assures that the quality of the sample used will be duplicative when future FDA inspectional samples are checked. GAO Report, "*Speeding Up the Drug Review Process*," HRD-82-16, 17 (Nov 23, 1981)

[30] 21 CFR §314.100(b)

[31] *Id* at §314.11. FDA does not review the safety of the inactive ingredient in the master file until the file is referenced by an NDA applicant for use in connection with an active ingredient. But FDA considers the safety of inactives to be a very critical part of its total drug safety decision. Brief for United States in United States v Generix Drug-Corp, No 81-1222 (US pending Oct 1982 Term)

[32] 21 CFR §314.100(d). Comparative claims of efficacy probably will not be permitted in the labeling, as a result of a 1982 fight between drug manufacturers concerning a disputed label claim. *Crout Signals an End to Comparative Efficacy Labeling*, 13 Wash Drug Letter 4 (Dec 14, 1981), " *Rx* Drug Comparative Promotional Claims", 44 F-D-C-Reports (Pink Sheet) 11 (July 26, 1982)

[33] Authority to approve is delegated at 47 Fed Reg 26822 (June 22, 1982)

[34] See §13.19

after the controversy has passed) to the division director level and the subdelegation has speeded approvals of the me-too product copies.[35] An "approvable" letter states that the application can be approved but that label and labeling copies must be submitted.[36] At this point, the firm prepares and FDA approves or modifies a "summary of safety and effectiveness" which is the publicly disseminated, summary basis of approval for the drug product.[37] Then the "approval" letter is sent and the drug may be marketed. A monthly list of approved drugs carries news of the approval.[38]

FDA has three controls after approval. The first advertisements for a prescription drug must be submitted to FDA and, thereafter, FDA can request that ads be submitted.[39] Pre-approval promotional efforts are strongly discouraged and can delay an approval.[40] Reports of adverse reactions must be submitted very rapidly to FDA during the first year after approval.[41] Problems of late reporting have led some firms into conflict with the FDA, while FDA has attempted in proposed rules to expedite all adverse reaction reports, first during the IND process[42] and later by requiring updating of adverse information after the filing of the NDA but prior to approval.[43] In some cases FDA imposes additional post-approval testing by agreement with the manufacturer—

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[35] Address by National Center for Drugs & Biologics Director H Meyer to National Association Pharmaceutical Manufactures, Dorado Beach, PR (Jan 16 1983)

[36] 21 CFR §314.100(d)

[37] *Id* at §314.14(e). Note that the total file is withheld. But factual internal memoranda of FDA reviewers would be available under the Freedom Of Information Act, *see* Sterling Drug Inc v Harris 488 F Supp 1019 (SD NY 1980)

[38] This listing is available by mail subscription from National Technical Information Service, Springfield, Virginia

[39] *See* Ch 15

[40] FDA has been adamant in opposing promotional information prior to marketing

[41] As the NDA-IND changes come into regulations format, rapid transmission of adverse reactions already provided for in 21 CFR §310.300 will be expanded. Address by HHS Secretary Schweiker to National Pharmaceutical Council (June 23, 1982)

[42] Adverse reaction data on investigational new drugs is extremely important. In its proposed rules, FDA would require IND holders to report within no later than 20 days an incident of adverse experience "that may suggest significant hazards, contraindications, side effects or precautions." 21 CFR §312.12(b)(1)(i) (proposed), 48 Fed Reg 26741 (June 9, 1983)

[43] The NDA reports are divided into immediate reports, 15-day reports, and 30-day reports, with those of least gravity taken into the annual report as well. 21 CFR §314.80(c) (proposed), 47 Fed Reg 46652 (Oct 19, 1982)

forcing agreement as the negotiated precondition for product approval where a doubt about safety or efficacy remains.[44]

The most common debates on new drug approval relate to efficacy. Safety screening steps in animal and basic human studies usually alleviate safety concerns or place the safety risks into perspective, from which therapeutic benefits can be said to outweigh risks, though as with all small-scale inquiries, safety information in test phases may differ from actual market experiences.[45] FDA is careful to get this safety information in as complete detail as possible, during the pre-approval phases, to assist in the final risk assessment. Failure to provide the date risks an enforcement action.[46] FDA has used many clinical guidelines for study methods,[47] and has recommended that these be used in the drug industry, particularly by generic firms which customarily are weak in the research field.[48] Efficacy controversies are usually scientific disputes about whether a study was adequately controlled, to avoid prejudice to the "blinding" of the research, and whether statistical tables of patient progress demonstrate that the drug had a significant advantage over the control placebo product.[49] FDA has devoted a great deal of attention to the adequacy of controls in a study to assure that the agency's scientists agree that the proof of

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[44] Special reporting obligations may be imposed, 21 CFR §310.304, and FDA actively sought approval of a Phase IV authority which would permit agency control of post-approval studies on the product, while drug reform legislation was pending in 1977-80. That additional reporting may be part of the 1983 regulations

[45] Because of the intentionally small number of persons exposed to a drug before it is marketed, each patient's experience will be carefully studied and there may be debates about reactions or effectiveness in a handful of patients, who represent one millionth of the numbers of patients who would be exposed after approval. FDA is very aware of the difficulty of predicting adverse reaction experiences and so is ready to control the new product after it enters the marketplace. Oraflex was a product marketed between May and August 1982, which was suspended from sale by its manufacturer as a result of adverse reaction reports received after FDA approval.

[46] Proposed 21 CFR §314.80, 47 Fed Reg 46652 (Oct 19, 1982)

[47] Preamble to Proposed NDA Revision Rules, 47 Fed Reg 46627 (Oct 19, 1982).

[48] Address by National Center for Drugs & Biologics Director H Meyer to National Association of Pharmaceutical Manufacturers, Dorado Beach, PR (Jan 16, 1983); Speech by Acting Commissioner Novitch to Conference on Generic Drugs (July 15, 1980); Testimony of Commissioner Hayes to Congress, FDA Appropriations: Hearings Before the Subcomm on Agriculture, Senate Appropriations Comm, 97th Cong 1st Sess (1983)

[49] FDA guidelines and the Good Clinical Practices rules control the experimentation

efficacy is well established. Courts uphold FDA in this complex area.[50] A product with no significant advantage over a placebo would not be effective enough to justify the product's risks to patients, and could deter the user from use of a product which would be effective.

FDA audits the data which are submitted in the NDA process as part of its bioresearch monitoring programs, such as those for clinical investigators[51] The use of foreign data as a basis for approval is permissible as long as some United States research supports the approvability conclusion and as long as the foreign data were compiled under standards acceptable to the FDA (which conclusions could be audited by FDA visits to that foreign testing site.[52] If the audits or the manufacturing site inspections are not satisfactory, there may be a delay in the approval of the product.[53]

Drug approval is a human process and humans tend to disagree at times. The NDA process includes a level of appeal which proceeds from the reviewer to the supervisory officials, to a committee which is headed by the Director of the National Center for Drugs and Biologics.[54] It is important that firms use their appeal rights, so that they

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[50] Courts have tended to be quite deferential to FDA in the "new drug" area, *see e.g.*, Weinberger v Hynson Westcott & Dunning 412 US 609 (1973); Rutherford v United States 442 US 544 (1979), and this has been especially true in the efficacy evidence area. *see e.g.*, Smithkline Co v FDA 587 F2d 1107 (DC Cir 1978); Edison Pharmaceutical Co v FDA 513 F2d 1063 (DC Cir) *rehearing denied* 517 F2d 164 (DC Cir 1975): but if the rules of efficacy are changed in midstream and approval is refused, the firm may be able to find a sympathetic court, Amer Cyanamid Co v FDA 606 F2d 1307 (DC Cir 1979). See also cases cited at Ch 15

[51] *See* 21 CFR pts 52 *et seq* and Ch 23

[52] Although FDA has permitted foreign data to satisfy Phases I and II, before the controlled double-blind efficacy studies, FDA has required at least one of the Phase III studies to be a United States study. 21 CFR §314.1(c)(2), item (12)(c). An exception exists for drugs intended to treat diseases which are rare in the United States. In 1974-80, 51% of new drug approvals for truly new drugs or indications contained foreign clinical studies, and of these 17% were studies deemed pivotal or significant for approval. Under a new policy revision, foreign clinical data may be the sole support for an NDA if the data are applicable to United States medical practice, if the investigators are of a "recognized competence," and if FDA deems those data valid without an on-site FDA inspection. *FDA Oversight Hearings Before House Comm on Govt Operations*, 97th Cong, 2d Sess (Aug 3, 1982) testimony of FDA Commr A Hayes)

[53] A firm which refuses inspection or fails to show that the facility is adequate to make the product will have a difficult time winning FDA clearance for its NDA

[54] *FDA Oversight Hearings Before House Comm on Govt Operations*, 97th Cong, 2d Sess (Aug 3, 1982) (testimony of FDA Commr A Hayes)

are not foreclosed from litigation for failure to exhaust administrative remedies.[55]

Public access to the drug approval process occurs when approval is announced and the summary of the data which served as a basis of safety and efficacy is made available.[56] The detailed information remains confidential; that which is released cannot be used as a basis for approval of another firm's subsequent products.[57]

The process for drug products which are "orphans," i.e., which have so little a market as to be unattractive for manufacturers' investments in research, is different. More FDA involvement with testing, potential involvement of other federal agencies like the National Institutes of Health, and possibly a relaxed efficacy requirement because of smaller test populations, will be some features of an orphan drug approval process.[58] It has been suggested that orphan products are so difficult to run through larger double-blind studies that FDA should accept expert opinions concerning efficacy, but the suggestion would be so different from normal FDA insistence on having two double-blind clinical studies that its future is questionable.[59]

The time for the NDA approval process is 180 days, by statute, from filing to final action.[60] Reforms within FDA have been made to reduce the perennial inability to abide by this time period.[61] But a court would uphold a reasonable delay and would side with the FDA

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[55] The comparable food additive clearance process produced the litigation in Stauffer Chem Co v FDA 670 F2d 106 (9th Cir 1982). Stauffer failed to exhaust its administrative remedies after an adverse opinion letter from FDA. In the NDA process, reconsideration opportunities already exist. 21 CFR §10.75. And *see* Dormer, *Contesting Adverse FDA Decisions: Is it Worth The Risk?* 4 Med Device & Diag Industry 26 (1982)

[56] 21 CFR §314.14

[57] "FDA Discussions of Unpublished Data," 44 F-D-C Reports (Pink Sheet) TG-7 (June 7, 1982)

[58] These are "orphans" because they lack sufficient commercial markets to justify the costs of development. FDA has set up an Office of Orphan Product Development to work with the Dept of HHS Orphan Products Board and the Pharmaceutical Manufacturers Association Commission on Drugs for Rare Diseases. *FDA Oversight Hearings Before House Comm on Govt Operations*, 97th Cong, 2d Sess (Aug 3, 1982) (testimony of FDA Commr A Hayes)

[59] "FDA Drug Efficacy Determinations," 44 F-D-C Reports (Pink Sheet) 3 (May 10, 1982)

[60] 21 USC §355(c)

[61] *FDA Oversight Hearings Before House Comm on Govt Operations*, 97th Cong, 2d Sess (Aug 3, 1982) (testimony of FDA Commr A Hayes), and *see also* Address by HHS Secretary Schweiker to National Pharmaceutical Council (June 23, 1982)

where injunctive relief to force approval is sought.[62] Measures to speed up the process have been under consideration for some time.[63]

§13.12 New Drug Applications: Investigational New Drug Exemptions

The investigational new drug exemption provisions of §505 of the Act are extremely important for drug firms to comprehend.[1] No new drug can be approved without first satisfying FDA about its safety and effectiveness in humans. To gather the needed evidence requires an *investigational new drug exemption application* (IND) which puts the FDA on notice of the proposed clinical trials. An IND is deemed approved if FDA does not object; usually, FDA has reviewed animal test results and the proposed program for the new drug's human tests within two months of the IND filing.[2]

Prior to the 1962 amendments, there was no IND system comparable to the present elaborate system; four lines in the Act, rather than the present page of text, discussed investigational new drugs.[3] But eleven birth defects cases in the United States which followed the widespread "investigational" use of an unapproved drug in the early 1960s, thalidomide, led Congress to write strict control authority into the Act.[4] The investigations issue entered the bill late, as a result of the publicity given thalidomide while the bill was in final stages of

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62 Newport Pharmaceuticals Intl Inc v Schweiker Food Drug Cos L Rep (CCH) ¶38148 (DDC 1981)

63 *Compare* Address by HHS Secretary Schweiker to National Pharmaceutical Council (June 23, 1982) *with* HEW Review Panel on New Drug Regulation, Final Report (1977) *and* Commission on the Federal Drug Approval Process, "Substantial Evidence Requirement Should be Reduced," 44 F-D-C Reports (Pink Sheet) 2 (Mar 2, 1982)

1 21 USC §355(i). This section has had a "profound effect" on United States and world drug development by its very existence in United States law. Crout, *The Nature of Regulatory Choices* 33 Food Drug Cosm LJ 143, 420 (1978)

2 21 CFR pt 312; and HEW Review Panel on New Drug Regulation, Final Report 19-23 (1977).

3 Before 1962, 21 USC §355(i) read simply: "The Secretary shall promulgate regulations for exempting from the operation of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety of drugs." Food Drug & Cosmetic Act ch 675, 52 Stat 1040, 75th Cong 3d Sess (1938)

4 Ley, *Federal Law and Patient Consent* 24 Food Drug Cosm LJ 520, 521 (1969)

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it GRASE. The issues are *quite distinct.* There may be opposing experts; the fact that FDA does not agree with the experts "does not eliminate the fact of their disagreement," and the plaintiff has the burden to establish such *generality* of recognition. *Chattem, Inc v Heckler* Food Drug Cos L Rep (CCH) ¶38293 (D DC May 10, 1985).

Add to text at end of section:

When is a drug the "same" drug? The answer depends on the context. In the case of orphan drug status, a court decided that the FDA properly treated two drugs as being different, and properly granted orphan drug status to one. Under 21 USC §360cc(a), orphan status will be exclusive once the NDA is granted, and this will exclude other products from the market. Thus, FDA approval is a reviewable decision when challenged by a third party whose drug would be excluded. On the substance of the issue, the court agreed with FDA that a biotechnological drug and a human extracted material which were used for the same purpose were not the same. The FDA's decision was upheld. *Genentech, Inc v Bowen* 676 F Supp 301 (D DC 1987).

The advocate should consider that exemptions may apply from new drug status, and case precedents on animal drugs might be applied to human drugs as well. FDA took what a court believed was an unreasonably narrow view of exemptions and an unreasonably strong demand for new animal drug restrictions. This would conflict with the statutory policy that FDA would not interfere with medical practice. FDA's view was rejected by the court. *United States v Algon Chemical, Inc* Food Drug Cos L Rep (CCH) ¶38079 (D NJ 1988).

§13.11 New Drug Applications: The Process

Add to footnote 1:

See economic analyses of the FDA approval delay problem, S Peltzman, The Benefits and Costs of New Drug Regulation (R Landau ed 1973); Schifrin, *Lessons From The Drug Lag: A Retrospective Analysis of the 1962 Drug Regulations* 5 Harv J Law & Public Policy 91 (1982).

Add to eighth line of text in carryover paragraph on page 13-62 at end of sentence:

Since enactment of §355(c) in 1962, FDA has considered the date of "approval" to be the date on which FDA issues a written notification

of a new drug's approval. *Mead Johnson & Co v Bowen* Civ No C-85-3971 (D DC Jan 27, 1987).

Add to text at end of second full paragraph, page 13-58:

The new drug approval requirement applies to both users and distributors of the new drug; there is no implicit exemption from §505 because one is an end user of a drug rather than a commercial firm. *Duncan v United States* Food Drug Cos L Rep (CCH) ¶38269 (WD Okla 1984).

Change Rutherford citation in footnote 50 to:

806 F2d 1455 (10th Cir 1986).

Add to text after note 57:

There was a great debate over this data's status in the early 1980's, with one court holding that it was not a trade secret but that it was *confidential commercial information. Public Citizen v FDA* 704 F2d 1280, 1291 (DC Cir 1983).

Congress ultimately settled the argument and determined that the data would be withheld, upholding the FDA administrative position that such data was properly confidential. Congress adopted at FDA's request a legislative determination that safety and efficacy data may be withheld by FDA upon a showing that commercial confidentiality helps the developing of secret research data maintain a stronger competitive position. Loss of exclusive use would cause a loss of competitive position, and under those *extraordinary circumstances*, FDA need not disclose the data when requests for disclosure are made under the Freedom of Information Act, Pub L 98-417, 98 Stat 1585 §104 (1984), and see O'Reilly, *Knowledge is Power: Legislative Control of Drug Industry Trade Secrets* 54 U Cin L Rev 1 (1985).

Add to footnote 58:

and as to orphan drug developments, see Grossman, *The Orphan Drug Act: Adoption or Foster Care?* 39 Food Drug Cos LJ 128 (1984).

Add to text at end of section:

FDA has the power, through a generic rule applicable to a number of drug applicants, to limit the applicants' access to certain regulatory entitlements which had been readily available in the past. *Upjohn Co v FDA* 811 F2d 1583 (DC Cir 1987).

ed the clause once it had been added to the legislation, and unanimous votes led to enactment on September 6, 1958.[12]

Problems with color additive products under the 1938 Act surfaced during the 1950s, when a reexamination of approved colors found that they could create human safety risks.[13] Legislation set safe limits on levels of colorants in finished foods, drugs, and cosmetics and established certification procedures for approval of batches of colors.[14] After the food additives debate, color additives legislation was adopted with relative ease, but it also included the Delaney anti-cancer clause.[15]

§3.07 The New Drug Amendments of 1962

The two principal conditions which historically have led to major food and drug legislation have been the existence of a persuasive leader with legislative skills, and the occurrence of a crises in which the weaknesses of existing protective legislation are exposed to the public by the news media. Harvey Wiley and the meat adulteration muckraking and Senator Royal Copeland and the elixir sulfanilamide incident were joined in 1962 by Senator Estes Kefauver and the thalidomide birth defects case. The result of that combination of efforts and events was a major revision of drug approval authority for the Food and Drug Administration.

The 1938 Act gave the FDA a negative option authority; it could act against drugs, but if it failed to act in a timely manner and did not use specific procedures, the drug would come onto the market despite any uncertainties as to its safety.[1] The statute failed to require proof

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LJ 460, 462 (1973). For other participants in the controversy, *see* Sunshine, *Regulatory Aspects of Food Additives—Yesterday, Today and Tomorrow* 31 Food Drug Cosm LJ 264 (1976) and Kleinfeld *supra* note 2 at 559

[12] Food Additives Amendment of 1958, Pub L No 85-929, 72 Stat 1784 (codified at 21 USC §348)

[13] Janssen, *FDA Since 1938: Major Trends and Developments* 19 J Pub L 205, 210 (1964)

[14] 21 USC §376

[15] *Id* at 376(b)(5)(B)

[1] To refuse to allow a drug application to take effect, FDA would have to hold a hearing and make findings in the form of an order; if no order were made, the application would become effective in 60 days, former 21 USC §355(c); but the secretary could delay action for up to 180 days from the date of filing. *See* Cavers, *The Food Drug & Cosmetic Act*

that drugs were effective, so the FDA was forced to approve implicitly a drug which had not been shown to be unsafe even though it may not have been effective for the use intended.[2]

Senator Kefauver's public hearings were a dramatic attack on prices and profits of the pharmaceutical industry.[3] Much of the original economic thrust of his efforts was effectively blunted by prudent defensive lobbying on the part of the pharmaceutical industry. Kefauver had spent a great deal of time on patent reform and the promotion of generic drug products and vigorously criticized advertising practices which failed to communicate adverse information about drugs and their side effects to physicians.[4]

The sponsors of legislation increasing the power of FDA over new drugs made much of the thalidomide incident. In that case a new drug marketed in Europe, but only available on a test basis in the United States, proved to be teratogenic with infants born with seal-like flippers instead of limbs.[5] Under the proposed legislation more time was to be made available to FDA's drug review staff, through extension of statutory time limits, to make decisions about new drug applications filed by drug firms.[6] More extensive safety and effectiveness testing would be required with efficacy tested through "adequate and well-controlled" studies. "Adequate tests by all methods reasonably appli-

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of 1938: Its Legislative History and its Substantive Provisions 6 L & Contemp Prob 2, 40 (1938)

[2] S Rep No 1744, 87th Cong 2d Sess (1962):

> In the first place, once the Food and Drug Administration determines that its value as a drug outweighs its toxicity, the Department claims that it must permit the drug to be marketed even though its claim to effectiveness is exaggerated. In the second place, where a drug is essentially innocuous, it must clear the drug despite the fact that its claim of effectiveness is not borne out by the evidence. . . . The Department believes that the manufacturer should satisfy the Food and Drug Administration that his product is effective for the purposes claimed before it is marketed.

Quoted in [1962] US Code Cong & Ad News 2892

[3] [1962] US Code Cong & Ad News at 2898, Kefauver: "[T]he record is clear that by any test and under any standard the prices of most drugs are excessive and unreasonable."

[4] Views of Senator Kefauver, S Rep No 1744, 87th Cong 2d Sess (1962)

[5] In the United States, over 2.5 million doses were distributed in investigations by 1,270 physicians. Comment, *The Food and Drug Administration: Law, Science and Politics in the Evaluation and Control of New Drug Technology* 67 NwU L Rev 858, 868 n 41

[6] 21 USC §355(c)

cable" would be required to determine the safety of drugs during the clearance process.[7] The burden of providing substantial evidence of effectiveness was placed squarely on the drug manufacturer, and a continuing post-approval reporting requirement was also imposed to maintain the flow of safety information.[8] Explicit records inspection authority was added for investigation of new drugs.[9]

A major compromise issue in the legislative development of the 1962 amendments was advertising, an issue which had been hotly contested in 1938 as well. The conference reconciled conflicting House and Senate views by rejecting mandatory FDA pre-approval of drug advertising for prescription drugs.[10] However, the conference report strongly encouraged prior review of such advertisements (without much future adoption of the encouragement) and limited the FDA's post-clearance power to act against advertising which it had already reviewed.[11]

Along with the drug approval authority and efficacy amendments, FDA received a number of incidental powers including power to register establishments and controls over antibiotic drugs.[12] As a concession to the Kefauver view on drug marketing economics, generic names for products were to be established by FDA and then disseminated on labeling in order to make the public aware of the identity of trademark-named drug products.[13]

A review of the amended statute's impact on technology drew

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[7] *Id* at §355(d)(1); subsection (d) defines "substantial evidence"

[8] *Id* at (j)(1); this had its origins in President Kennedy's letter of April 10, 1962, to the chairman of the Senate committee studying drug amendments: "Drug manufacturers should be required to keep records on and report to the Department of Health Education & Welfare any indications of adverse effects from the use of a new drug or antibiotic." *See* [1962] US Code Cong & Ad News 2896

[9] 21 USC §355(j)(2)

[10] [1962] US Code Cong & Ad News 2933-34

[11] It is the intention of the managers on the part of the House . . . that no action shall be brought by the Secretary under this section because of the use of an advertisement submitted to him prior to publication and found not to be in violation of this paragraph, unless he subsequently finds the advertisement in violation, advises the advertiser, and allows reasonable time to effect the necessary correction.
Id

[12] 21 USC §§357(h), 360

[13] 21 USC §358; *see* Conference Report adopting Senate version, [1962] US Code Cong & Ad News 2932

this conclusion from the 1962 amendments: "Among federal agencies undertaking technology assessment, the FDA is unique in that its sole responsibility is to determine whether the benefits to be gained by releasing a new technology outweigh the risks inherent in that innovation."[14]

Unlike other comparable agencies the FDA was given no responsibility, formal or informal, for promoting the particular aspect of technology which it must regulate.

As neither an advocate of technology nor absolute arbiter of legal status—to the extent that courts retain that role—the FDA was placed in a unique position by the 1962 drug amendments. Readers may draw their own conclusions about the consequences of the use and abuse of FDA's powers since those important amendments. Congress set up procedures with which the agency subsequently disagreed; FDA felt that individual hearings could not be practicably implemented, and the Supreme Court agreed.[15] Historical fact suggests that the procedural amendments of 1962 were soon obsolete as the agency became conscious of the mass of implementation work. Historians of the 1990s will record the ultimate value of those amendments for the FDA and for society.

Between the new drug amendments and the medical device amendments of 1976, FDA underwent a consolidation of existing statutory authorities which expanded the bounds of the statute. Animal drug authority, the Drug Listing Act, and an amendment resolving a long-standing dispute over labeling and sale of vitamin and mineral foods were adopted during the period from 1962 to 1976.[16]

§3.08 Medical Devices Amendments

Of the statutory categories created by the 1938 Act the one left

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[14] Comment *supra* note 5 at 870

[15] The Supreme Court dismissed the procedural fine points of the amended act's hearing provisions with the comment:

> The deluge of litigation that would follow if 'me-too' drugs and OTC drugs had to receive de novo hearings in the courts would inure to the interests of manufacturers and merchants in drugs, but not to the interests of the public that Congress was anxious to protect by the 1962 amendments. . . .

Weinberger v Bentex Pharmaceuticals, Inc 412 US 645 (1973)

[16] Act of Apr 22, 1976, Pub L No 94-278, 90 Stat 401

all cases, except in the situation in which an OTC drug may be unsafe unless it is placed on prescription as a manner of controlling distribution.[12]

§14.04 Definitions: Safety

Safety is not an absolute determination; its boundaries are the current knowledge of science and its assumptions are the normal behavior of man. Water is safe except when ingested in large quantities by swimmers; salt can have toxic effects at very high levels. The judgment of marketability made by both the manufacturer and the Food and Drug Administration for a drug product takes into account the benefits of the product and the relative risk presented in light of other available remedies and the particular therapeutic situation to which the drug is addressed.[1] Even dying patients, if the status can be defined, are entitled to be protected from drugs which are not "safe", and are denied access to those drugs which may be unsafe, as the Supreme Court decided in the laetrile anticancer case in 1979.[2] And the proof of safety is not an easy assignment by any means.[3]

When FDA set out to define *safety* as it applies to drugs studied in the over-the-counter (OTC) drug review, it declared:

> Safety means a low incidence of adverse reactions or significant side

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[12] The need for prescription drug distribution in lieu of stronger label warnings has been debated in a 1978 administrative hearing, Matter of Supplemental New Drug Application, Benylin Expectorant, Docket 76N-0485 (FDA 1978), and see Parke Davis & Co v Califano, Food Drug Cos L Rep (CCH) ¶38132 (6th Cir 1977)

1 [T]he typical issue for the FDA is not the absolute safety of a drug. Most drugs are unsafe in some degree. Rather, the issue for the FDA is whether to allow sale of the drug, usually under specific restrictions. Resolution of this issue inevitably means calculating whether the benefits which the drug produces outweigh the costs of its restricted use.

Hess & Clark Division of Rhodia, Inc v FDA 495 F2d 975, 993 (DC Cir 1974)

[2] United States v Rutherford 47 USLW 4724 (June 18, 1979)

[3] "Proof of a drug's safety is . . . problematic . . . because of the uncertainty as to what constitutes an adequate demonstration of safety. Drugs that are toxic for a small number of patients may be perfectly harmless for the great majority of users . . . . Because all drugs induce some chemical reaction . . . no drug can be termed absolutely safe." Note, *Picking Your Poison: The Drug Efficacy Requirement and the Right of Privacy* 25 UCLA L Rev 577, 585-86 (1978). But see United States v Rutherford 47 USLW 4724 (June 18, 1979)

> effects under adequate directions of use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability.[4]

FDA then defined the term as subject to proof by "adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended or suggested conditions of use."

Congress intended that *safe* have the ordinary meaning of an absence of harmful consequences.[5] A perplexing regulatory problem has been to define safe in the abstract.[6] FDA's legislative approach in 1978-79 drug reform proposals was to find a product safe whose health benefits "clearly outweigh" its risks.[7] But "how much risk is acceptable in light of the beneficial effects likely to be achieved"[8] remains a difficult calculation. Former FDA Chief Counsel Richard Merrill stated the quandary:

> FDA is asked to apply the label 'safe' to compounds whose hazards are imperfectly understood and, in some cases, recognized to be serious, even if infrequent . . . (FDA) has been given this responsibility by a public that assumes a product it has determined to be 'safe' has no prospect of producing harm.[9]

It is important to underscore the term which acts as a qualification on the statute's misbranding prohibition against unsafe drugs: ". . . when used in the dosage, or manner or with the frequency or duration prescribed, recommended, or suggested in the labeling

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[4] 21 CFR §330.10(a)(4)(i); and see 37 Fed Reg 85 (Jan 7, 1972)

[5] *See* Merrill, *Can FDA Do Anything Right?* 2 Va Law School Report 20 (1978); Report by the Commissioner of Food and Drugs on Findings and Recommendations of the Review Panel on New Drug Regulation 95 (1978)

[6] Rutherford v United States 582 F2d 1254 (10th Cir 1978) *revd* 47 USLW 4724 (June 18, 1979)

[7] *See* S 1045, 96th Cong 1st Sess (1979), and S 2755, 95th Cong 2d Sess §109(e) (1978): "[T]he term 'safe' means that the health benefits of the drug entity clearly outweigh the risks presented by the drug entity, taking into account the standards and requirements applicable to drug products eligible to be licensed under the monograph . . .". The definition includes several factors to be considered as well, which may change as the legislation is debated

[8] Merrill *supra* note 5

[9] *Id* at 20

thereof."[10] Intended use controls how we can and do measure the safety of a drug, as that intention is manifested in directions in the labeling.[11] A drug is shown to be safe in the context of its recommended uses, *not* in the abstract.[12]

A prescription drug which bears full warnings is more likely to obtain prompt NDA approval for distribution than one which may be dangerous to the public if mistakenly misused.[13] But, as FDA's administrative law judge has opined, "questions of the safety of a drug when it is used in a manner contrary to the label warnings can be considered only in limited circumstances."[14] FDA bears the burden, according to that 1978 ruling in the Benylin proceeding, to demonstrate a reasonable possibility of misuse in violation of label instructions, if the agency wishes the safety-related issues which are not labeled to be considered in a safety decision.[15] Generally, misuse is not a major part of clearance considerations other than for a "controlled substance" drug. The 1978-79 drug law revision proposals would grant FDA more authority to include these misuse considerations in drug approvals and in decisions on continued approval.[16] It would "make clear that safety is always a relative matter — that using any drug always presents some risks that have to be weighed in the light

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[10] A drug is misbranded if "it is dangerous to health when used in the dosage, or manner or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof." 21 USC §352(j)

[11] United States v 62 Packages . . . Marmola Prescription Tablets 48 F Supp 878 (WD Wis 1943) *aff'd* 142 F2d 107 (7th Cir 1944) *cert denied* 323 US 731 (1944)

[12] *See* Initial Decision, Matter of Supplemental New Drug Application Benylin Expectorant, Docket 76N-0483 (FDA 1978) and *cf* Pharmaceutical Mfrs Assn v Richardson 318 F Supp 301, 313 (D Del 1970)

[13] 21 CFR §330.10(a)(4)(vi) presumes that a drug will be for over-the-counter sale unless risks are found to be associated with it. See Initial Decision, Benylin Expectoran., Docket 76N-0483 (FDA 1978), and Parke Davis & Co v Califano 564 F2d 1200 (6th Cir 1977) *cert denied* 435 US 942 (1978)

[14] Initial Decision, Benylin Expectorant, Docket 76N-0483, slip opinion at 7 (FDA 1978)

[15] *Id* at 8: "Consideration of safety evidence relating to uses of a drug outside of the label requirements necessitates a showing that there is a reasonable probability that such non-label indicated uses can be expected to occur."

[16] S 1045, 96th Cong 1st Sess (1979), and S 2755, 95th Cong 2d Sess §109(e)(2)(C) (1978); and "the risks of a drug include the risks from improper use and the societal risks that are presented by the drug." Department of HEW, Section-by-Section Analysis, Drug Regulation Reform Act of 1978 (1978)

of the benefits."[17] These proposed bills, however, were still in serious doubt in the 1979 session.

§14.05 Risk—Benefit Decisions in Drug Approvals

No drug is absolutely safe.[1] There will be some condition or circumstance in which any drug can cause harm to some susceptible individual. The societal role of the Food and Drug Administration is to make tough choices about which risks are acceptable in order to obtain a drug's benefits.[2] In making these risk—benefit judgments, a great deal of guesswork is inevitable. Animal tests and controlled clinical experiments do not always detect the problems which mass distribution of a drug would disclose. For the Bureau of Drugs, predicting and then balancing risks and benefits in a fair and equitable manner is the prime objective of the drug approval exercise.[3]

Safety decisions since the 1962 Drug Amendments have included exacting review of the benefits promised for a drug. Because Congress believed FDA's safety control of new drugs was satisfactory, the only change made was the addition of an effectiveness consideration.[4] Prior to 1962, benefits were considered only in those cases in which the drug was a serious part of life-saving therapy, the failure of which would

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[17] Remarks of Secretary Califano, HEW Press Conference on Drug Regulation Reform Act of 1978 at 5 (Mar 16, 1978)

[1] Hess & Clark Division of Rhodia, Inc v FDA 495 F2d 975, 995 (DC Cir 1974); Rutherford v United States 47 USLW 4724 (1979); and see generally Merrill, *Compensation for Prescription Drug Injuries* 59 Va L Rev 1 (1973)

[2] FDA's rationale for the 1978 proposed drug amendments stated: "[T]he decision on whether a drug can be used for medical care in the United States is a risk-benefit determination. The definition of 'safety' [in S 2755] reflects long-standing practice in evaluating drugs for approval . . . . Every drug — even aspirin — presents some risks. If 'safety' were defined to mean the absence of any risk, then no drug could be approved." Department of HEW, Section-By-Section Analysis, Drug Regulation Reform Act of 1978 (1978). *Cf* Hutt, *Public Policy Issues in Regulating Carcinogens in Food* 33 Food Drug Cosm LJ 541 (1978)

[3] Crout, *The Nature of Regulatory Choices* 33 Food Drug Cosm LJ 413 (1978); Hutt, *Philosophy of Regulation* 28 Food Drug Cosm LJ 177 (1973); and see Note, *The Food and Drug Administration: Law Science and Politics in the Evaluation and Control of New Drug Technology* 67 NwU L Rev 858 (1973)

[4] *See* Senate comments, S Rep No 87-1744, 87th Cong 2d Sess (1962), [1962] US Code Cong & Ad News 2890

jeopardize patients' survival.[5] The Act does not permit explicit decisions about comparative benefits to be used in safety decisions, but implicitly the agency tends to weigh the net additional benefit to practitioners of a new drug against the extent to which a drug presents more possible hazards than its existing counterparts.[6] During the drug approval process, promotion of innovation per se is not considered, apart from therapeutic benefits which may merit a faster "track" of approval, since FDA's mission is not one of technology improvement.[7]

Congress, the overseer of FDA performance, has been a vigorous watchdog of drug safety for years, partially because of posturing for attractive headlines, and partly from sincere concern that the public was not getting the protection that it deserved.[8] Funds to improve conditions and personnel levels at the Bureau of Drugs' drug-review team level, though often requested, have been chronically short.[9]

Though Congress, of all possible decisional sources, is *least* able to make scientific judgments, it holds a short leash on its delegated authority for FDA approval of new drugs: "One recurrent message [from Congress] is that it is always safer for agency officials to prevent the marketing of products that entail physical risk—regardless of what benefits they prove. No FDA official has ever been publicly criticized by a member of Congress for *refusing to allow* the marketing of a drug." But many have "paid the price of public criticism, sometimes accompanied by an innuendo of corruptibility, for approving a product that could cause harm."[10]

Observing the risk—benefit process through the eyes of Congress, all risks should perhaps be eliminated to maximize the political acceptability of the approval decision. Viewed through the eyes of medical specialists at FDA, approvals may seem a tedious and adversarial process. Advisory committee discussions of the pending drug

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5 *Id* at 2891, and see Durovic v Richardson 479 F2d 242 (7th Cir 1973) *cert denied* 414 US 944 (1973)

6 Review Panel on New Drug Regulation, Final Report 62 (1977); Nouce of Opportunity for Hearing, Phenylbutazone, 42 Fed Reg 39141 ¶A-3 (Aug 2, 1977); and *cf* Holland-Rantos Co, Inc v United States Dept HEW 587 F2d 1173 (DC Cir 1978)

7 Note *supra* note 3

8 Merrill, *Can FDA Do Anything Right?* 2 Va Law School Report 22 (1978)

9 Review Panel *supra* note 6 at 45-47; Merrill *supra* note 8 at 22; and see Report by the Commissioner of Food and Drugs on Findings and Recommendations of the Review Panel on New Drug Regulation 84-85 (1978)

10 Merrill *supra* note 8 at 22

application,[11] internal disagreements among FDA toxicologists, chemists, pharmacologists, and other scientists[12] over details of the approval process, and often conflicting scientific judgments[13] lengthen the process of approval. A recent additional complication is the openness for decisionmaking within the Bureau of Drugs, which strives for a sort of consensus[14] among employees. The HEW study of the new drug approval process extensively examined the complaints about that process which were raised by the bureau's "conscientious objectors,"[15] whose complaints precipitated several years of external and internal evaluations of the process of drug approval.[16] Recently, still another player in the approval "game" has been added, with the emergence of therapy groups such as epilepsy organizations and the American Heart Association to spur the FDA toward approval of new therapeutic products for their respective areas of interest. This was the case with informal lobbying for approval of valproic acid in treatment of epilepsy in 1978.[17]

The most difficult of all regulatory decisions, and drug approval decisions, are those in which potential carcinogenic or other chronic effects may be present but cannot be confirmed by present human evidence.[18] Though this text is not of sufficient length to cover these complex issues, a reader interested in risk—benefit and relative risk theories would do well to begin with the literature on cancer causation,

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[11] For a good brief statement of the current NDA process, *see* Review Panel, *supra* note 6 at 23-25

[12] *Id* at 31-32; the Review panel found that industry had not dominated the reviewing staff, as had been alleged, to resolve these disagreements in industry's favor

[13] Conflicting views are frequent and led to FDA action to formulate a dissenter policy. *see* Report by the Commissioner *supra* note 9 at ix

[14] *Id* at viii-ix

[15] *Id* at x-xi

[16] Merrill *supra* note 8

[17] HEW Press Release P78-12 (Feb 28, 1978). Commissioner Kennedy obliquely acknowledged the legislative oversight pressure of the epilepsy patient organizations when he remarked that "new drugs are not approved by referendum"

[18] For an example of an extremely difficult approval decision by the FDA in this field, examine the animal drug Sensitivity of Method (SOM) debate reflected in a 1979 pronouncement, 44 Fed Reg 17070 (Mar 20, 1979): "[T]he Commissioner now believes that the time is ripe for formulating a comprehensive approach for regulating all chemical carcinogens." And see aspartame notice of Board of Inquiry, 44 Fed Reg 31716 (June 1, 1979)

including both the legal[19] and political[20] aspects as well as the scientific causation theories. It is so particularized an examination that no useful brief statement can be made to distill the thousands of pages written about cancer causation in recent years.

§14.06 Warning Labels

A drug must bear adequate warning labels to communicate its dangers.[1] The sole exception to this rule applies to prescription drugs in retail containers for which a physician has given directions for use.[2] Warning labels enable the consumer to avoid overdoses of habit-forming or toxic drugs,[3] and permit the consumer to know of drug interaction problems which may be present with certain drugs. As the interactions of smoking and alcoholic beverages with drugs become better known, for example, drug warning labels can be expected more frequently to caution against smoking or drinking while under medication.[4]

If label warnings can be simply and directly stated, and protect the consumer effectively, then their use on the drug should obviate the need for prescription-only distribution. Only in limited circumstances can FDA base a decision on the safety of a drug when it is misused in defiance of proper labeling.[5] Considerations of improper use as a

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[19] Hutt, *The Basis and Purpose of Government Regulation of Adulteration and Misbranding of Food* 33 Food Drug Cosm LJ 505 (1978)

[20] Carter, *How to Assess Cancer Risks* 204 Science 811 (May 25, 1979)

[1] 21 USC §352(f)(2)

[2] *Id* at §353(b)(2), and exception from §352(f)

[3] Secretary of Agriculture recommendations following the Elixir Sulfanilamide disaster, §13.02, stated: "Much injury results from insufficient directions and from insufficient directions and from lack of warning against overdosage, or administration to children, or use in disease conditions where the drug is dangerous, or possibility of drug addiction." Senator Copeland, the 1938 Act's principal sponsor and a homeopathic physician, noted that pain relievers sometimes led to overdosages in "pathetic instances" because "there is always a temptation on the part of a human being to think, 'If a little medicine will help me a good deal, more will help me still more.' " Senate Debate (Mar 9, 1937). Both are *quoted in* C. Dunn, Federal Food Drug & Cosmetic Act 1326 and 744, respectively

[4] *See e.g.*, Oral Contraceptive Patient Labeling, 43 Fed Reg 4214 (Jan 31, 1978)

[5] Initial Decision, Matter of Supplemental New Drug Application, Benylin Expectorant, Docket 76N-0483 (FDA 1978), and see United States v Article . . . Decholin 264 F Supp 475 (ED Mich 1967)

Tab 62

RISK WATCH

The Odds of Life

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New York, New York • Bicester, England

6

Medical and Surgical Risks

The title of this chapter could serve for a 1500-page textbook of medicine and surgery, but our aim here is more modest. It is to illustrate some of the important ways in which treatment-associated risk is identified and measured in contemporary medicine. Coronary heart disease and hypertension are two major diseases considered in some detail. Coronary bypass surgery is prominent in the treatment of CHD, and the problems of its evaluation compared to drug treatment illustrate a whole class of treatment-related risk-assessment problems. The treatment of hypertension, on the other hand, is an area where the insurance perspective is uniquely strong, allowing a striking comparison between the risks of treating and not treating. Then we examine the process by which prescription drugs are tested. Drugs are the mainstay of modern medicine, and so the limits on risk detection in drug testing have wide impact on treatment-related risks. Here the comparative risks of treating versus not treating reveal some curious quirks in how small risks can become the basis of big controversies, while big risks go unnoticed. To begin, however, it is useful to understand the limits on the individual physician's ability to detect treatment-related risk.

Risk as Perceived by the Individual Physician

There are natural limits on the individual physician's ability to perceive treatment-related risk. These limits have to do with the size of any one physician's practice.

To understand the origin of those limits, consider how a busy practice operates. If the physician works six 10-hour days a week and

Risks Related to Drugs and Drug Regulation

Twentieth century technology has transformed two old institutions, the doctor and the drug, from relatively harmless comforters and anodynes into powerful forces capable of strong actions, good and bad. Drug regulation in the United States appeared in three successive steps: (1) in the first years of this century, following a number of deaths due to a contaminated vaccine; (2) during the 1930's, following a number of deaths due to a sulfa drug product that was formulated with a toxic solvent; (3) in 1962, following the recognition that thalidomide was responsible for children being born with deformed limbs. All three steps focussed on tightening standards of manufacturing, testing, and labeling to minimize the risk of adverse reactions; the most recent big changes added for the first time the requirement that drugs be proven effective for uses claimed for them by their manufacturer.[5]

Each country has its own special approach to drug regulation, but the economic and technological power of the United States is such that the activities of the Food and Drug Administration (FDA) are closely watched internationally, and frequently imitated by other countries, though each country brings a special character to their drug regulatory system: the Japanese are extremely rigid; the Americans demand complete documentation of every aspect of the drug's testing program, irrespective of the mountain of paper—and cost—entailed; the British are sensible and flexible; the French have a system which is a unique amalgam of the bureaucratic and the personal; the Germans and the Canadians lean heavily on the FDA's policies.

The bias in all drug regulatory systems is toward preventing unexpectedly hazardous drugs from reaching the market. That bias is understandable from the history of how drug regulation came into being, through public reactions to a series of disastrous incidents involving relatively small numbers of victims compared to other hazards in our lives. This bias poses a curious paradox, as illustrated by the following rather simple-minded parallel. We disrupt traffic and incur rather special risks to rush injured or seriously ill people to the hospital by ambulance so that they can come as quickly as humanly possible to the best available treatment, and sometimes we bend heaven and earth to rush a special medicine to a few people who

need it. Yet somehow none of this sense of urgency carries over to the regulatory review of new drugs.

An example of the cost in human lives of the slow pace of the drug regulatory system is the seven years it took for FDA approval from the time of the first publications showing that administration of beta blocker drugs reduced mortality in the first few years after heart attack. The results of the first clinical trials were reported in 1974, and in 1976 the Swedish regulatory authorities approved this use for one of the beta blocker drugs—alprenolol—then already available in the Swedish market. The first FDA approval of this usage for a beta blocker came in November 1981. In 1975, Professor William Wardell of the University of Rochester had called this beneficial action of the beta blocker drugs to the attention of the then-commissioner of the FDA, Alexander Schmidt, together with calculations indicating that each year's delay in approving this use would cost about 20,000 lives.[6] Six years after Wardell's letter, when the first approval finally came, FDA Commissioner Arthur Hayes announced that, indeed, the newly approved product would save 17,000 lives per year. Nobody thought to haul him up to the Capitol, sit him down in front of the TV cameras and a Congressional investigating committee, and ask him what about the 100,000 people who died in the time between the first publications and the approval, without which few physicians will use a drug. In effect, Americans had to use ONURONE for a half dozen years even though something demonstrably effective was already available.

Yet, when it recently developed that there had been five deaths from allergic reactions associated with the widely used analgesic drug ZOMAX, there was a strong reaction in Congress and the launch of an investigation to learn how this terrible thing had been allowed to happen to the American people.

Critics of drug regulation point out that the only time that Congress, the President, and the American people were of one mind in praising the FDA was when Dr. Frances Kelsey delayed the approval of thalidomide in the United States. President John F. Kennedy transformed her into a heroine by presenting her with a special medal in the White House Rose Garden. The message was not lost on her colleagues at the FDA or in other regulatory agencies around the world: there is no credit to be gained for lives saved due to speedy regulatory action, but a very small number of fatalities or other

severe adverse reactions to a drug will lead to public humiliation and scorn for any regulatory official who may have acted other than very cautiously and conservatively in reviewing the drug.

If one were to judge the overall value of drug regulation strictly on a body-count basis of lives lost due to regulatory delays as against lives saved due to keeping unduly dangerous drugs from the market, one would have to question seriously whether drug regulation is a very good bargain. With little or no regulatory involvement, many other industries design, test, manufacture, and market complex products on which many lives depend, and it would appear that both competitive forces and the pressure of product liability lawsuits are effective checks on the sale of unduly risky products. At the very least, we ought to be a sophisticated enough society to be able to see and understand the risks that are prolonged, as well as the risks that are minimized, by regulatory review. A simple-minded stranger looking in might wonder: if we have ambulance crews on duty around the clock and allow them to run red lights when called, should we not have our drug regulatory agencies working a three-shift, seven-day week to minimize the fatal consequences of delaying the introduction of improved drugs?

The FDA and other drug regulatory agencies around the world get most of the criticism whenever the subject of long delays in bringing new drugs to market arises. However, there are two other often overlooked factors that contribute to these delays. One of these is that only large pharmaceutical firms can mobilize the resources to develop and test a new drug, but one of the inevitable consequences of large size in any organization is that it necessarily becomes slow and bureaucratic in its operation. The second delaying factor is a technological one. As pharmacologists and physicians have become increasingly cognizant of the power of modern drugs, the processes for testing new drugs have become increasingly elaborate and searching. There has been a steady expansion in the kind and number of animal toxicologic tests run on new drug candidates, and the whole field of designing clinical trials has been fundamentally transformed during the last two decades. Thus, the whole process of new drug development is vastly more complex and time-consuming since the days when insulin was rushed from the laboratory to the bedside. It is probably amenable to some considerable pruning, but there is little incentive in the current regulatory environment for that to happen.

In clinical trials of various treatments, one seeks to standardize diagnostic criteria and methods, to standardize the severity of disease in the patients admitted to the trial, and to standardize the various treatment regimens which the trial is designed to compare. Standardizing the cooperation of the patients with the prescribed regimens, however, is easier said than done—even when everyone acts in the best of faith and solemnly swears to do just what the doctor asks.

Clinical trials have come to play an increasingly important role in modern medicine, putting different treatment methods to the test of quantitative comparison in as controlled a fashion as ethical medical practice allows. When a new treatment modality appears for a previously untreatable disease, the controlled clinical trial will naturally include a no-treatment group, though often disguised from patients, nurses, and doctors by use of a placebo, i.e. an ONURONE treatment. Contemporary standards of ethics mandate that participants in the trial know they are in a trial and be informed about the various treatments that they may (or may not) actually receive. The designs of such studies are a not-always judicious blend of scientific experiment and everyday medical practice.

There are many vexing problems in the design and execution of clinical trials, but they are one of the very important advances which have come into clinical medicine in the last quarter-century. Their routine use in the evaluation of virtually all new methods of treatment—plus their use in the retrospective assessment of many time-honored methods of treatment—is gradually transforming medicine from an almost wholly empirical art to an amalgam of quantitatively validated technology and art. Clinical trials are gradually providing the main outlines of how the best practice should be carried out, but clinical judgement and the art of medicine continue to guide most diagnosis and treatment. Thus, the physician's judgment will continue to be an important element in the risk of disease, however much it may seem that technology may have displaced the art of medicine and the essential human contact between patient and physician or nurse. In medicine, the patient is an object of a discipline which, in using technological-scientific procedures, puts on a scientific face but is both more and less than a science in the extent to which it draws on the art of human judgment tempered by experience.

The growth of medical knowledge based on well-designed clinical trials is a slow process. Clinical trials take a great deal of time to plan,

to be reviewed by the necessary disinterested individuals for ethical concerns, to find the appropriate patients to enter into the trial, to carry out the sequence of treatments called for, to analyze the data, and finally to communicate the data to other physicians and health care personnel. There are pitfalls in the process, many of which come down to bending the need for scientific rigor to the exigencies of caring for patients. The trial has to have enough rigor to give a definite answer to the question of which treatment modality is best, or the better of two; at the same time it has to be a close enough approximation of routine clinical practice so that treatment efficacy shown in the trial will also be found in practice. Some big clinical trials take three to five years to complete, especially if they involve questions about diseases that progress slowly.

Yet there is a huge numerical gap between even the largest of clinical trials and the potential patient population that would use a new drug. Some of the biggest trials are those in which contraceptives were evaluated: these have had between 10,000 and 25,000 participants. Most new drugs, however, are tested in 1000–2000 people. In the case of the oral contraceptives, there are about 12 million women in the United States using these products and probably upwards of 50 million worldwide. In the case of drugs for hypertension, there are about 40 million hypertensives in the United States. Certainly not all will ever take any one drug, but, if a drug appears to be especially efficacious and well tolerated, and poses little risk, it may be used in half or more of the patient population. Consequently, the clinical trial population and the population who may use the product in the market will differ in size by hundreds of thousands to millions. That number gap has the important consequence of making the first few years' use of the drug after market introduction into a big but poorly controlled experiment.

The initial years of market experience are necessary to close the number gap between the population size in the clinical trial and the population size needed to define safety-degree to the 4–5 SDU range (i.e. risks of 1 adverse reaction in 10,000 to 100,000 patients). This point has already been mentioned in the discussion on oral contraceptives in Chapter 5, but it is a very important fact of life about which our society manages to delude itself. To illustrate why the number gap exists, suppose the clinical trials have involved 5000 patients, which is an unusually large number; if 50 patients have

similar adverse reactions, it is reasonably certain that the risk of that adverse reaction can be defined as 1 in 100 during the time period involved. Suppose, however, that only one patient develops a particular kind of adverse reaction. It is difficult to know what to conclude about a single event—it may or may not be related to the drug, and so the matter has to be held in abeyance until more experience is gained with the drug. Thus, having 5000 people in the clinical trial does not allow definition of a risk level of 1 in 5000, but something rather more like 1 in 1000.

Suppose five patients developed similar adverse reactions in a group of 5000 patients: one has an approximate idea that the risk is 1 in 1000. This figure is only an approximation, however, for it may be that there was a chance clustering of a few "extra" adverse reactions within the study group and that the true risk is less. On the other hand, the events in the study group may somehow have minimized the occurrence of the adverse reaction, such that in subsequent market experience with the drug, the adverse reaction turns out to occur at a 2–5 times greater incidence than in the trial. As a practical matter, the biggest unicohort size one can define with reasonable accuracy in a clinical trial is about one-fifth the size of the trial's population. If, however, the patients in the trial have to be considered as being divided into subgroups—by age, sex, other disease conditions, etc.—then the biggest unicohort definable will be about one-fifth of the biggest subgroup.

The initial use of the drug in the first year or two after its market introduction builds up large numbers of users—assuming the product is widely prescribed—and will necessarily begin to reveal adverse reactions which occur at the 1 in 10,000 to the 1 in 100,000 level of incidence. As in the clinical trial phase of experience with the drug, it is not possible to draw any conclusions from a single adverse reaction. Therefore, it usually takes 4–6 occurrences before an association with the drug is suggested. However, one of the things lacking in the United States is a means of insuring that adverse reactions to drugs are reported; as a result, more than nine-tenths go unreported. Thus, it may take over 2 million people's use of a drug before the full extent of its risk is reasonably well defined to the 1 in 50,000 level—per use if it is an acute-use drug, per year if it is a chronic-use drug. If we had a mechanism in place that insured efficient and timely reporting of adverse drug reactions in the first years after a new

product entered the market, we could reduce both the number gap and the time required to identify drug-related risk. Even with an efficient system of reporting adverse drug reactions, however, there will still be a large number gap between the biggest clinical trials and the smallest numbers needed to reveal all the risk information we crave to know about any widely used drug.

Therein lies one of the reasons for saying that life is an experiment: there is no earthly means to finance or manage a clinical trial that could define the degree of drug safety to more than 3 SDU (1 adverse reaction per treatment period in 1000 patients). Yet our social and political behavior indicates that we reserve the right to react with shock, horror, and witch-hunting when drug-related risk shows up at the 3–4.5 SDU level (1 in 1000 to 1 in 30,000).

The number gap is a fact of life, but it is not generally understood. When a newly introduced drug is associated with adverse reactions, there is usually a big uproar and witch-hunt—talk of prosecuting people in the company which developed the drug, suspicious congressional cross-examination of FDA people who reviewed and approved the product, and a usually brief but intense coverage of the subject by the news media. By the time media attention shifts to a fresh subject, the drug in question usually has acquired such a widespread reputation as a poison that it is practically useless thereafter. Many months or years later, when the nature of the association has been worked out and reported within professional circles, the news media give little attention to the resolution of the story, which sometimes exonerates the drug.

The automobile manufacturers seem to be able to recall their products without such catastrophic losses in credibility, but drugs are much more politicized, despite the fact that automobiles kill many more people than drugs do.

For example, McNeil Pharmaceutical recently recalled, on its own initiative, its pain-relieving non-narcotic drug, ZOMAX, for re-evaluation in light of a small but growing number of reports of serious and very rarely fatal allergic reactions to the drug. There were five known fatalities possibly attributable to use of the drug, which had been widely prescribed and so had a very large cohort of past and present users. Prior to McNeil's voluntary recall of ZOMAX, the recall of a drug because of possible adverse reactions had meant the drug's end as a product. McNeil's stated intention,

however, was to clarify the risk situation and then decide whether to reintroduce the product, and if so to make changes in instructions to physicians and patients which would act to minimize risk. This "recall for re-evaluation" was a bold and innovative step, signifying a new degree of realism in evaluating the risks of adverse reaction to a widely used drug.

However, a congressman promptly demanded an investigation of what the FDA had done wrong, what the company had done wrong, and so forth, effectively taking the matter out of McNeil's hands and turning it into a media happening. The concept of a "recall for re-evaluation" is ethical, scientifically sound, and beneficial to the public health, but no pharmaceutical company is likely to repeat McNeil's experiment for a long time to come. Instead, recalls will continue to be postponed until adverse reactions are clearly occurring at a risk level which is high enough to force everyone involved to jettison the product permanently. This policy means that: (1) we shall continue to lose opportunities to preserve useful drugs by making risk-reducing changes in their instructions for use; (2) more people will have to suffer adverse reactions to trigger a permanent recall than a recall for re-evaluation.

An intriguing and not yet fully understood footnote to the ZOMAX episode was revealed about eight months after McNeil's voluntary withdrawal. A prescription-event monitoring study of ZOMAX in England showed that patients taking the drug appeared to have about half as many heart attacks and strokes during their time on the drug as would have been expected for their age group. After the drug was withdrawn and the patients all had to turn to other drugs for pain relief, the rate of heart attacks and strokes resumed at the usual rate.[7] If this unexpected finding is in fact related to the use of ZOMAX, it would certainly suggest that many more premature deaths were prevented by the use of the drug than it may have caused, if even the worst assumptions about its risk were true. The basic fact is that drug use, both in clinical trials and in everyday medicine, is a risk discovery process. Clinical trials can only screen for relatively high-risk problems at the 1–3 SDU level; the discovery of the more dilute risks—at the 3–5 SDU level—has to occur in the course of the drug's use in everyday medicine.

Useful new drugs do not grow on trees, but now cost an average of $70 million and take seven to ten years each to develop. Every new

stricture in the heavily politicized arena of drug regulation adds new layers of cost and time. Each new layer of cost effectively raises the minimum patient population size for which drug development is economically justifiable. The term "orphan drugs" has recently appeared. These are drugs for diseases that affect too few people to allow a return on the expense to develop, test, and register the drug product. The orphan drug phenomenon has been created by successively more complex and costly regulations governing new drug development.

Pharmaceutical innovation is a goose that has laid many golden eggs in the past half century. One cannot but wonder how hard the process can be squeezed before investment simply moves into other areas,[8] leaving it to governments to develop the new drugs. Reviewing the meagre pharmaceutical innovations which have come out of the state-run industries of Eastern Europe does not inspire one to believe that this would be a very effective way to meet present and future disease challenges.

Not all the news is bad, however, as a drug gains use-experience in the market, for sometimes unsuspected new therapeutic uses are identified for older drugs—the above-mentioned apparently favorable action of ZOMAX, for example. Once the initial several million patients have used the drug and its overall risk picture is reasonably well-defined, these new uses are indeed bonuses. They do cost money to document in clinical trials and to gain approval from regulatory authorities for inclusion in the indicated uses for the product. These costs pose a major problem when the discovery of a new use comes at or after the end of the drug's patent life, for thereafter the drug is public property, and a new claim registered by any manufacturer is more or less automatically available to all. That quirk in the regulatory and patent laws deprives all manufacturers of the economic incentive to innovate with older drugs, which is one reason why most manufacturers will opt to bring forward a new, "me-too" drug of the same class as the older one, around which to develop new uses. That has two disadvantages: (1) it keeps the regulatory system clogged reviewing "me-too" drugs; (2) each new drug raises a whole new set of risk questions, which can only find minimal answers in clinical trials. Because of the number gap, about 2 million patients have to undergo the involuntary experiment of testing for adverse

reactions that occur at the 3–4.5 SDU level (1 adverse reaction per treatment cycle in 1000 to 50,000 patients).

One area of recent pharmaceutical innovation which partly sidesteps this problem is the development of new drug delivery systems, or therapeutic systems. These are special dosage forms which meter the drug into the body at low, usually steady rates for extended periods of time. They have their own patent protection and thus can be used in conjunction with some older drugs to develop better tolerated, less frequently dosed forms while still relying on the existing risk definition of the drug that came from its initial years in the market. Controlling the rate of entry of drug into the bloodstream can have an important influence on balance between therapeutic actions and side-effects of many drugs. These new drug delivery systems make it both scientifically and economically possible to extend or improve the uses of some older drugs. Examples of such products are the "skin patches" which administer nitroglycerin for angina, scopolamine for motion sickness or vertigo, clonidine for hypertension, and estrogen for the menopausal syndrome and to prevent postmenopausal mineral loss from bones. These technological advances are gradually turning the major pharmaceutical companies away from their long-standing, single-minded focus on new chemicals as the sole means of pharmaceutical innovation.

Everyone should understand that there is no such thing as a risk-free drug, just as there is quite obviously no such thing as risk-free surgery. It is unfortunate that the term "drug safety" is used so widely in so many contexts, both lay and professional, for it is fundamentally misleading and contributes to the confused politicization of pharmaceuticals. U.S. drug regulations require that the "safety and efficacy" of each new pharmaceutical product be proved, thereby implying promise of the unattainable goal of absolute safety. German regulations avoid the confused semantics of the term "safety," and ask instead that the product should be "free of concern," which is also unrealistic, for how can any intelligent person be "free of concern" in the face of a defined risk of death or serious injury? The choice of words in these two sets of drug regulations symbolize the lack of realism and confusion with which we, as technologically advanced societies, confront risk. Often while we dither, patients are left with ONURONE.

Part of clinical judgment is to balance risk and benefit in the use

of a drug. With great insight, Plato used the term *pharmacon* to mean both "medicament" and "poison," leaving it to the context to indicate which meaning was appropriate. It is not always easy to make such judgments in clinical practice, nor can these judgments be made "free of concern." The use of an effective anticancer agent may necessitate—and warrant—the acceptance of a 1 in 10 risk of fatal bone marrow suppression, but when the antibiotic chloramphenicol turned out to have a 1 in 30,000 risk of fatal bone marrow suppression, its previously general anti-infective use was promptly restricted just to the treatment of typhoid fever, for which it was uniquely effective and still offered an overwhelming advantage compared to other treatments.[9] A diuretic drug called tienilic acid had to be withdrawn several years ago when it turned out, after its first half-year in the U.S. market, that its use carried a 1 in 500 risk that the patient would develop a sometimes fatal liver disorder;[10] curiously, the same drug had already been in the market in France for several years without this problem having become evident, nor was there any evidence that it was occurring in France when very careful studies were done there after the problems became known in the United States. That discrepancy remains a mystery. Aspirin is probably the most widely used drug of any—a recent British survey showed that 4.5 million out of the 57 million total population took it at least once a week, and half a million people took five or more a day.[11] Aspirin has its recognized risks—among them are gastrointestinal bleeding and ulceration, plus precipitation of asthma attacks in people with a certain kind of allergy problem—but the risks of these occurrences are very dilute. However, the exceptional person who has encountered an adverse reaction to aspirin is well-advised to use another agent in the future.

The most troublesome kind of adverse effect of a drug is the one which takes many years to appear. Two examples will illustrate. The first is an antidiarrheal drug, clioquinol, which had been widely used in many countries for many years throughout the world before its use in Japan was associated with several hundred cases of serious neurological damage, blindness, and a number of deaths.[11] Protracted investigation has failed to give a satisfactory explanation for how this catastrophe occurred when and where it did, but an extensive litigation process put the blame on the drug and held the pharmaceutical companies involved liable. The second example is a true "time

bomb"—diethylstilbestrol (DES). This artificial estrogen compound had been developed in the 1930's; among its clinical uses during the 1940's and 1950's was the treatment of impending miscarriage. In the late 1960's a small number of young women in Boston were found to have a previously extremely rare form of vaginal tumor; case-control analysis showed that during the fetal lives of these young women their mothers had received DES treatment for impending miscarriage. In earlier years, this choice of treatment had been especially strongly advocated within Boston medical circles, which probably accounts for why the problem was first recognized in Boston, instead of elsewhere. Other—seemingly minor—abnormalities in the genital tract are also observed in about 1 in 3 of either males or females exposed to DES in fetal life; fortunately, the lifetime risk of developing the vaginal tumor in the exposed females appears to have been about 1 in 7000 (3.8 SDU).[12] The whole story will not be known, however, until the people exposed during fetal life have lived their entire lives.

There is no conceivable clinical trial or drug regulatory mechanism which could have prevented either catastrophe. Both could, of course, have been prevented if, back about 1900, all countries had legislated against administering synthetic chemical substances to humans, just as we can readily prevent jet plane crashes by banning jet planes. The cost in human suffering and in premature death of restricting our pharmacopoiea to the ONURONEs of the 19th century would create such a preposterous imbalance of risk and benefit that there can be no alternative to accepting occasional disasters as part of the price of improved lives and health for the vast majority. Nor should we delude ourselves that drugs extracted from natural sources—plants or animals—offer any inherently greater insulation from risk, for every natural substance has its undesirable, frankly toxic, and sometimes lethal actions.

The only hope for minimizing the risk of such events in the future is the added understanding that we gain with each passing year from the big investment being made in biomedical research. It may eventually enable us better to foresee certain kinds of problems and avoid having always to deal with them in retrospect.

We have been lucky to have gained so much and lost so little as modern technology has moved so rapidly into medicine. Infrequent disasters involving small numbers of people have brought govern-

ments into the process in the name of protecting the public health. We should pay much more attention than we now do to the health consequences of the slow pace of pharmaceutical innovation and regulation, for the resulting forced dosing with ONURONE can be responsible for many thousands of premature deaths. The whole area of medicine and drugs is so thoroughly politicized that the foreseeable changes will probably bring both a slower pace and more governmental involvement, not less. An important area for improvement is the monitoring of unexpected drug actions—both adverse and beneficial—during the drug's use in the first few million patients. Improved monitoring would reduce the number gap standing between risks definable in clinical trials and risks acceptable to society.

Tab 63

Therapeutic implications of the drug lag

The American lag with respect to Britain in the introduction of new therapeutic drugs over the past decade was analyzed to determine whether, in therapeutic terms, Britain has gained or lost from adopting the more permissive policy. The therapeutic impact of a new drug on the whole community is difficult to assess, mainly because there are few methods or data available for measuring benefit. On the evidence currently available, Britain probably did not lose appreciably from the introduction of ineffective drugs, nor from the fact that a greater number of new drugs were made available. The main deleterious effect was that Britain suffered more toxicity due to new drugs than did the United States, as could have been anticipated from the fact that more new drugs were marketed there. However, considering the size of the total burden of drug toxicity, the portion due to new drugs was extremely small, and would in any case be at least partially offset by the adverse effects of older alternative drugs had the latter been used instead. Conversely, Britain experienced clearly discernible gains by introducing useful new drugs, either sooner than the United States or exclusively. On balance, Britain appears to have gained in comparison from its more permissive policy toward the marketing of new drugs coupled with a more rigorous program of postmarketing surveillance. Wider issues raised by this study include the desirability of further intensifying postmarketing surveillance, particularly in the case of new drugs; the conflict between the presently conceived public health role of a regulatory agency and the desire of a physician to choose optimal therapy for particular patients; the therapeutic and social implications of the control of drug utilization as distinct from marketing; and the significance of the latter controls for the future of medicine.

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In two previous papers of this series,[73, 74] the extent of the American lag in the availability of new therapeutic drugs was defined, and was shown to be accompanied by differences in therapeutic approaches in Britain and the United States. American physicians were found to be poorly informed about drugs used widely and for some years abroad but not yet available in the United States.

The present paper examines the therapeutic implications of that international difference. Compared with the United

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but this argues for a need for more knowledge and perseverance, rather than for fewer drugs.

In economic terms, the conclusion of the main study to date by Peltzman[54] is clear. Peltzman estimated that the effect of the 1962 amendments to the Food, Drug and Cosmetic Act has been to cost the American consumer at least $250 to 350 million annually, or about 6% of total drug sales. Peltzman's argument was in absolute terms. Since regulation of the drug development process has become more rigorous in Britain also since 1962, some losses may have been incurred there as well. But Peltzman's argument dealt with areas in which, as shown in the present study, Britain appears to stand favorably in comparison with the United States. It is probable, therefore, that British patients have gained economically in comparison with Americans.

In addition to economic factors, one should consider the influence of drug regulatory policies on the existence and innovative output of the research-based pharmaceutical industry, which has been responsible for most advances in drug therapy.

Lasagna[24] has reviewed the literature that points to a steep rise over the past decade in the cost of developing a single new drug entity in the United States, and the inhibitory effect that this may be having on the industry's willingness to explore new areas where remuneration may not be clearly foreseeable. The time required for a drug to undergo the necessary testing and pass through the regulatory review process is an important factor in the cost of development, and so the "drug lag" has a bearing on this cost.

A recent study of the economics of the pharmaceutical industry in Britain was performed by the Economic Development Committee for Chemicals, at the invitation of the Minister of Health following a recommendation along these lines contained in the Sainsbury Report on the pharmaceutical industry and the National Health Service. In the report of this study[55] it was noted that one of the factors contributing to the attractiveness of the United Kingdom for the development of a pharmaceutical industry was the system for the registration of new medicines. The report also, however, noted that the continuing attractiveness of Britain would depend on (among other factors) "maintenance of the system for the registration of new medicines in its present reasonable and non-bureaucratic form under the new statutory arrangements."

Conclusions

Three general conclusions emerge from this study about the processes of developing and introducing new drugs and about the differences between the British and American approaches.

The first conclusion concerns the effects of the "drug lag," based on the evidence currently available.

As Lasagna[24] has pointed out, the protection conferred by delaying the introduction of new drugs needs to be weighed against the therapeutic losses thus incurred. From the present study, it is clear that each country has gained in some ways and lost in others. On balance, however, it is difficult to argue that the United States has escaped an inordinate amount of new-drug toxicity by its conservative approach; it has gained little else in return. On the contrary, it is relatively easy to show that Britain has gained by having effective drugs available sooner. Furthermore, the costs of this policy in terms of damage due to adverse drug reactions have been small compared with the existing levels of damage produced by older drugs. There appear to be no other therapeutic costs of any consequence to Britain. In view of the clear benefits demonstrable from some of the drugs introduced into Britain, it appears that the United States has, on balance, lost more than it has gained from adopting a more conservative approach than did Britain in the post-thalidomide era.

The second conclusion relates to the

relative attention given to ascertaining a drug's safety in the earlier phases rather than in later phases of its development. Toxicity testing in animals can never guarantee a drug's safety in man[72]; neither can the small numbers of closely monitored patients required for premarketing trials of efficacy guarantee its safety in the population at large. Given these facts, the actions of a regulatory agency should hinge to a large degree on the quality of postmarketing surveillance. If postmarketing surveillance is poor or nonexistent, then the decision to approve a new drug is a grave and irreversible one; it should be delayed as long as possible (forever?) in the hope that exhaustive preclinical and clinical testing, together with the experience of other countries, will reveal all unsuspected toxicity in the drug before it is approved for marketing. If, on the other hand, postmarketing surveillance is rigorous enough to detect even rare drug toxicity promptly, then drugs could be introduced more rapidly, with confidence that (provided information from the surveillance system is acted upon at once) no widespread harm to the community will ensue even if the drug does turn out to induce unsuspected reactions.

It should be recognized that, contrary to general belief, the early stages of new-drug investigation are extremely safe.[11] When widespread, catastrophic drug toxicity has occurred, it has only been after a drug has been marketed, and never in the early phases of development. There is a tendency for episodes of this nature to be taken as evidence of laxity in the drug-approval process; however, in the present regulatory era when preclinical tests are being used to the limit of their usefulness (and possibly beyond), it would be more correct to regard widespread toxicity as a failure of postmarketing surveillance, rather than a failure of premarketing screening.

Therefore, if the resources available to develop and regulate new drugs are not unlimited, the way these resources are currently deployed should be re-examined. Rather than continually raising the animal and human premarketing hurdles, society might benefit more from ascertaining and improving the predictive power for man of animal safety tests, and from intensifying postmarketing surveillance. The latter approach appears to be a major difference in practice between the current drug regulatory systems in the United States and Britain. In the United States, animal and premarketing procedures are generally more demanding; implementation of the regulations requires a large number of people; and assessment takes a relatively long time. Nationwide postmarketing surveillance is, however, poorly developed by international standards. In the United Kingdom, the premarketing requirements are less onerous, and new drug applications are processed more quickly with a considerably smaller staff.[54, 62] Conversely, Britain is compelled to place more reliance on its more sophisticated surveillance system, and this approach appears (with the reservations made earlier) to have forestalled widespread toxicity due to the introduction of new drugs. As already discussed, Britain appears on the evidence currently available to have benefited from this approach.

The third conclusion is that fundamental differences can be discerned in the roles of the regulatory agencies in Britain and in the United States, and that these differences carry profound implications for the practice of medicine.

In the United States, proof of the efficacy of a proposed new drug has been a formal requirement of the approval process since 1962, when efficacy was formally added to safety by the Kefauver-Harris amendments to the Food, Drug and Cosmetics Act. Before 1962, evidence of efficacy, although not formally required, was in fact given some weight.[56] It is, indeed, entirely reasonable in principle to merge the question of efficacy with that of safety, since no toxicity is tolerable if a drug lacks efficacy.

In Britain the main formal focus of the drug approval process from 1963 until 1971

Tab 64

15 March 1985, Volume 227, Number 4692

SCIENCE

Benefits, Risks, Vaccines, and the Courts

The hero of the 1500's was an explorer who blazed trails through hostile terrain to discover new worlds and wealth. The "hero" of the 1900's is a victim who blazes trails through hostile lower courts to establish a new precedent for lawsuits and wealth.

The high cost of such thinking is that few manufacturers want to make vaccines any more (see *Science*, 1 March, p. 1012). The profits are small; the risk of lawsuits very great. The country may soon be in the ludicrous position of developing a vaccine for AIDS and of not being able to find a manufacturer to produce it.

How have we strayed so far from the days of the 1700's when Zabdiel Boylston inoculated his son and friends to protect them against smallpox? Boylston inoculated 247 people with live pox, of whom 6 died—that is, 1 in 41. He was reviled by the medical profession and others. Then an epidemic occurred in which the remaining 241 survived while 1 in 7 of the general population died. Today Boylston is considered a pioneer, and the risk in vaccination is 1 in 100,000. Yet a lawsuit settlement in the millions of dollars for the one victim removes the incentive to protect the 99,999.

Boylston's heroic experiment had a risk ratio that would not be acceptable under today's regulatory codes. Those codes—considered too lenient by some, too strict by others—are at least based on some rational and statistical design. The lawsuit, however, is usually decided on highly emotional grounds, the poor victim against the infinitely wealthy government or corporation. Who would be so cruel as to deny a few millions here or there to a crippled victim or a bereaved family? Yet the result of such compassion is to deny protection to the many.

The dilemmas are large, and real. A probability of 50 children getting permanent brain damage after receiving vaccine against diphtheria, pertussis, and tetanus (DPT) is heartbreaking, even weighed against 3.5 million children inoculated. The control experiment has been done, however. When the DPT vaccine fell into disuse in England and Japan during the 1970's the death rate shot up (for example, during one 2-year period in England 36 children died per 100,000 who were infected with whooping cough). Various forms of legislation are being considered, but the approach of having the government subsidize whatever the courts allow, either to companies or to victims, seems unworkable. If a federal judge can order a drug company to pay $10 million to a single victim, $8 million punitive damages, what will the judgments be when the federal government is the ultimate underwriter?

It is not appropriate to shield companies or the federal government from punishment for lax or incompetent procedures. It is appropriate, however, to face the reality that a conscientiously executed procedure for making vaccines will still produce some tragic side effects. Do we continue to act out a play in which any bad result must have a villain, or do we face the reality that modern vaccines have great benefits and some built-in risks?

At some point the judicial system will have to face the most inexorable of all laws, the law of probability. Risks of diseases and harmful side effects from vaccines are steadily being reduced, but they will never be absolutely zero. Damage from industrial accidents involved lengthy court battles until the Workmen's Compensation Act was passed. With drugs and vaccines, some national compensation system in which medical costs, lost pay, and so on are calculated on an appropriate statistical basis will need to be enacted. The law would of necessity exclude extra compensation for emotional trauma and the life-style to which the lawyer has become accustomed. Such a law could allow moderately priced vaccines to be produced with appropriate compensation calculated into the price on an actuarial basis. Then we may be able to introduce into government the concept of a statistical morality as the foundation of a more rational approach toward all compensation situations. The next hero may be the statistics advocate who has the courage to say, "The healthy can afford to help the sick, but we do not live

Tab 65

continued from page 1537

vaccines and accompanying host factors. Wyeth HDCV is a subunit vaccine, disrupted with tri-(n)butyl phosphate and further inactivated with β-propiolactone, while Merieux HDCV is a whole virus vaccine inactivated with β-propiolactone. Other factors, including older age, receipt of mildly immunosuppressive medications and administration of the vaccine into the buttocks, may also have contributed to the lower responses. Injections in the gluteal region will almost always be delivered into fat.[6] It is not known whether there is a difference in absorption of the two types of HDCV when administered by this route. It has recently been recognized that administration of hepatitis B vaccine in the gluteal area probably results in a poorer response than vaccination in the deltoid.[7] It is recommended that all adult immunizations be administered in the deltoid region[8,9]; the deltoid area is the preferred site for HDCV vaccination. The gluteal area remains an acceptable site for large volumes of RIG. HDCV and RIG should never be administered in the same anatomic sites.

One 1.0-mL intramuscular booster with Merieux HDCV in the deltoid area is recommended, based on review of available information, for all persons who have been potentially exposed to rabies since Oct 15, 1984, and who have received postexposure prophylaxis with Wyeth HDCV (unless serum samples obtained after postexposure prophylaxis demonstrated an acceptable antibody titer). Merieux HDCV can be obtained by telephoning (800) 327-2842. Anyone currently receiving Wyeth vaccine should complete the course with Merieux vaccine and does not require an additional booster. Serologic testing is recommended if a systemic allergic reaction (serum sickness or urticaria) occurred during previous administration of postexposure prophylaxis. In that case, an acceptable serologic response obviates the need for a booster vaccine dose. Serum testing continues to be indicated if a patient who received postexposure prophylaxis with HDCV is immunosuppressed (by diseases or medications).[1] State health departments can be contacted for the addresses of laboratories where serologic testing is available.

The Wyeth vaccine administered preexposure and in the recommended 1.0-mL intramuscular doses (three injections) has been effective in inducing antibodies. Based on currently available information, persons so-vaccinated need neither serologic testing nor booster doses of HDCV, except for those select groups previously identified.[1] In the event of future exposure to rabies, persons who have received preexposure prophylaxis with either type of HDCV should receive two 1.0-mL intramuscular booster doses of HDCV (one each on days 0 and 3), as is currently recommended.[1]

*At present, the CDC considers a neutralizing antibody titer that produces complete inhibition in the rapid fluorescent focus inhibition test at 1:5 dilution or greater (1:11 or greater by the Reed-Muench method) an acceptable response to immunization.[1] The World Health Organization considers 0.5 IU/mL or greater[2] an acceptable response (approximately equivalent to 1:56 by the Reed-Muench method or complete inhibition at the 1:25 dilution).

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Diphtheria-Tetanus-Pertussis Vaccine Shortage

On Feb 12, 1985, the American Academy of Pediatrics hosted a meeting to discuss ways of dealing with the current shortage of diphtheria-tetanus-pertussis (DTP) vaccine. The meeting was attended by representatives of the American Medical Association; American Academy of Family Practice; the vaccine manufacturer; state, county, and city health officials; the US Department of Defense; and the US Department of Health and Human Services.

Available information indicates that, overall, state health departments have approximately 2.3 months' supply of DTP vaccine on hand, but this vaccine is not uniformly distributed, with 18 states having supplies on hand of one month or less. Because of close inventory monitoring and prudent use of DTP reserves held by the manufacturer, vaccine has remained available in the public sector to date.

A survey conducted by eight different state health departments of 583 physicians indicated approximately one third had had difficulties in obtaining DTP vaccine, and approximately one half were following the current recommendations to defer the DTP doses for 18-month-old and 4- to 6-year-old children. In four states, where inventory estimates were made, physicians' current inventories ranged from 1.9 to 2.9 months' supply.

Lederle Laboratories reported the release for distribution of one DTP vaccine lot on Feb 12. This lot, about 35,000 vials (525,000 doses), has been divided among the company's five regional distribution centers located in Los Angeles, Atlanta, Chicago, Philadelphia, and Dallas. This vaccine is being distributed to health-care providers now.

Because currently available supplies of DTP vaccine are limited, the manufacturer is carefully coordinating the distribution of vaccine to both public and private health-care providers. Following extensive discussions, the group reached the following conclusions and recommendations:

1. Current information indicates that adequate supplies of DTP vaccine should become available in mid- or late 1985.

2. Until adequate supplies become available, it is important to continue the currently recommended

practice of deferring the DTP vaccine doses for 18-month-old and 4- to 6-year-old children to assure that the initial three-dose immunization schedule for infants is met.

3. Practitioners should not administer partial doses of DTP vaccine in an effort to make the vaccine go further, since the degree of protection afforded by such partial doses is not certain.

4. Diphtheria-tetanus vaccine should not be substituted in the routine DTP vaccine schedule for 18-month-old and 4- to 6-year-old children.

5. It is important for practitioners to establish recall systems to ensure that children whose doses are deferred are recalled for the DTP vaccine they need once supplies become available.

6. Because some children will have their 18-month or "preschool dose" of DTP vaccine deferred this spring and summer, it may be necessary for day-care centers or school systems to allow provisional enrollment of such children until they can receive the needed doses.

7. As soon as adequate supplies become available, the Academy of Pediatrics and the US Public Health Service will notify physicians so they can again resume the full DTP immunization schedule and recall those who need additional doses.

Reported by US Public Health Service Interagency Group to Monitor Vaccine Development, Production, and Usage.

Ansamycin LM427

Since October 1983, the CDC's Division of Tuberculosis Control, Center for Prevention Services, has supplied the experimental drug, ansamycin LM427, under a "compassionate" investigational new drug permit to physicians treating patients with serious mycobacterial disease unresponsive to conventional therapy. Beginning Monday, Feb 18, 1985, physicians requesting the drug for new patients should contact the CDC Drug Service at (404) 329-3670 during normal working hours. Ansamycin LM427 is not released at night or during weekends. The Division of Tuberculosis Control ([404] 329-2530) will continue to provide medical consultation on the treatment of mycobacterial diseases.

Hemolytic-Uremic Syndrome Associated With *Escherichia coli* 0157:H7 Enteric Infections—United States, 1984

During the first 11 months of 1984, seven cases of hemolytic-uremic syndrome (HUS) associated with *Escherichia coli* 0157:H7 gastroenteritis were identified in the United States. All patients had microangiopathic hemolytic anemia, thrombocytopenia, and evidence of renal disease; none had new onset of neurologic abnormalities to suggest thrombotic thrombocytopenic purpura. A diarrheal illness preceded onset of HUS in all seven patients. The cases occurred in Washington, Nebraska, and North Carolina.

Washington.—Three cases occurred between March and October. The first two patients (women ages 25 and 36) had a prodrome of hemorrhagic colitis; the third patient (a 3-year-old boy) had a prodrome of watery, nonbloody diarrhea. *E coli* 0157:H7 was isolated from the stool of each patient. No exposures common to all patients were identified.

Nebraska.—During an outbreak in September of diarrheal illness caused by *E coli* 0157:H7 among residents of a nursing home, one of the patients with hemorrhagic colitis, a 63-year-old woman, subsequently developed HUS.

North Carolina.—During an outbreak of gastroenteritis (both bloody and nonbloody diarrhea) in a day-care center in September and October, three children who had bloody diarrhea subsequently developed HUS; they were 11 months, 31 months, and 35 months of age. *E coli* 0157:H7 was isolated from the stools of four ill children, including one with HUS.

Reported by Washington Dept of Social and Health Svcs; Div of Health, Nebraska State Dept of Human Resources; Div of Health Svcs, North Carolina Dept Human Resources; Enteric Diseases Br, Div of Bacterial Diseases, Center for Infectious Diseases, CDC.

Editorial Note: *E coli* 0157:H7 was first recognized as an enteric pathogen during the investigation of two outbreaks of hemorrhagic colitis that occurred in Oregon and Michigan in 1982.[1] Since then, *E coli* 0157:H7 has also been associated with sporadic cases of hemorrhagic colitis and HUS in the United States, Canada, and Great Britain.[2-4] Isolation of this very rare *E coli* serotype from stools of patients with HUS suggests that this pathogen may be one important cause of HUS; however, further epidemiologic and laboratory studies are needed.

Since *E coli* isolates from stool cultures are not routinely serotyped, the diagnosis of *E coli* 0157:H7 infection cannot be made unless physicians consider it and arrange for serotyping. Stools from HUS patients who present with a diarrheal prodrome should be collected as soon after onset of illness as possible and held frozen at −70 °C (−94 °F). Arrangements for examination of the stools and/or *E coli* isolates from such stools at state laboratories or the CDC can be made through state laboratory directors.

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Tab 66

Robert Windom *announces a framework for industry and government collaboration on an AIDS vaccine.*

collaborative program. These include: peptides isolated from or based on AIDS virus proteins that might be used in a potential vaccine, organisms such as vaccinia virus that can be genetically engineered to produce proteins normally made by the AIDS virus, methods for producing and dectecting the AIDS virus, isolation methods for proteins made by the AIDS virus, and molecular clones of the AIDS virus. The United States government owns the rights to these patents.

The PHS notice calls for collaborative plans from the private sector to be submitted by October 21, sixty days from the date of the notice. Each plan will be considered on a case-by-case basis, and final selection will be made by the agencies of the PHS including the National Institutes of Health and the Centers for Disease Control.

Harmison says that the concept for establishing a collaborative framework for AIDS vaccine development is not new. In 1984, the PHS issued an invitation for private industry to become involved in making test kits to detect AIDS virus antibodies in the blood (which were on the market by 1985), and the idea for vaccine development collaboration began then.

An AIDS vaccine is not likely to be available for general use until well into the 1990's. The primary reason for the expected delay in its development is the scientific complexity of the research problem, which necessitates large and equally complex research collaborations. Why did the PHS release its new notice now? Because the stage of scientific research warrants such collaborations at this point, says Harmison, and perhaps because the time is ripe for exercising some control over who has access to patent licenses. ■

DEBORAH M. BARNES

(A discussion of the different research strategies now being used to develop an AIDS vaccine will appear in the 12 September issue.)

Bankrupt the Company That Makes It?

In the present climate of richly rewarding lawsuits by individuals against manufacturers for product liability, U.S. pharmaceutical companies may be less than eager to invest large amounts of money and effort into producing a vaccine for AIDS. But an experimental AIDS vaccine should be available for initial clinical testing within the next decade, and individual scientists as well as drug companies recognize the need for legislation that will encourage rather than discourage vaccine production.

"The important legal issue is pretty clear," says Brian Cunningham, vice president and general counsel for Genentech in South San Francisco. "As the law stands today, manufacturers are held liable for injuries caused by a vaccine even though they were not negligent in designing it. In these circumstances, in my opinion, the legal system has simply run amuck. And for a small company like Genentech, we simply cannot take the financial risk." Genentech is now in the research phase of developing a potential AIDS vaccine, but the company has not decided whether it would move into full-scale vaccine development.

Currently, drug companies are subject to strict product liability, a legal term meaning that the manufacturer is liable for any injuries caused by the product, even though the product was made properly.

California is leading the legislative effort to lessen a manufacturer's liability for an AIDS vaccine with a bill, which is expected to pass before 1 September. Governor George Deukmejian has formally endorsed the vaccine legislation (as of this writing). His office projects that Californians will pay about $3.5 billion in medical costs alone for AIDS patients in 1990, making the need for a vaccine a financial as well as a health care issue.

Due in part to persistent lobbying efforts by Genentech and other pharmaceutical firms, the new bill would relieve drug companies from strict product liability. Introduced by assemblyman John Vasconcellos, it is designed specifically to apply to an AIDS vaccine once it has been approved by the Food and Drug Administration (FDA). The bill offers not only protection from two classes of liability claims, but also provides incentives for drug companies to make a vaccine for AIDS.

The California bill has four essential features. First, it leaves intact a person's right to sue because of injury due to manufacturing defects in an AIDS vaccine. At the same [illegible] strict product liability in a suit based on warning or design defects if the vaccine has been found to be "unavoidably dangerous" (defined on the basis of a California appellate court decision as a product with great public benefit that is unavailable in a less dangerous form). Second, it states that it is the intention of the state of California to purchase 750,000 doses of the vaccine for a maximum of $20 a dose, if this number is not sold in the 3-year period following FDA approval of a vaccine. Third, it provides for $6 million in grant money to be given to drug companies that do clinical testing of potential vaccines. And fourth, the bill guarantees compensation to individuals injured by an AIDS vaccine by paying their medical expenses, lost income, and a capped amount for pain and suffering. The money for this compensation fund will come primarily from a surcharge that the vaccine manufacturers will pay, with any future state appropriations to be decided later.

The California bill may prove to be model legislation for other states or perhaps for the federal government. The House of Representatives subcommittee on health and the environment has introduced bills that pertain to childhood vaccines. One of them, sponsored by subcommittee chairman Henry Waxman (D–CA), would protect pharmaceutical companies that make childhood vaccines which are already FDA-approved against strict product liability. It would also offer compensation to children who are injured by a properly made vaccine.

But any forthcoming vaccine for AIDS is admittedly experimental and will not have FDA approval until it is shown to be both safe and effective. Whether protective legislation will be introduced at the federal level for such an experimental vaccine is uncertain. Public Health Service scientists and representatives from private industry have been discussing these issues with congressional staff. ■ DEBORAH M. BARNES

NASA Council Sees Continued Erosion of Space Program

The advisory council of the National Aeronautics and Space Administration (NASA) has expressed "great concern" about the agency's ability to fulfill its mandate for national preeminence in space.

In a blunt letter to agency administrator James C. Fletcher, dated 14 August, council chairman Daniel J. Fink also says "that actions being taken by the U.S. to restore its

Tab G

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Food and Drug Administration because they are not considered drugs. There is no solid information about the correct dosage that might alleviate arthritic tenderness or to keep cholesterol and triglycerides at their correct levels.

So what should the American public do when these wonderful fish oil omega-3 capsules are offered to them at a high price? It's still best to get fish oil from eating fish.

The FDA should take a good hard look at all nutritional supplements, including fish oils, and exert some authority over them based on the claims being made.

Q. In one of your columns you described a pill that women could take to terminate an early pregnancy. Can you tell me when this drug will be marketed in this country and what is holding it up?

A. The name of the drug is Mifepristone and will stimulate a spontaneous abortion (miscarriage) in 90 percent of women when taken before the fifth week of pregnancy, studies say.

I believe this drug will never be marketed in the United States. Although it will be opposed by the anti-abortion lobby, the main reason probably will be the inability of any manufacturer to obtain product liability insurance.

Q. Do you think because Nancy Reagan has had breast cancer that there will be a faster development of a drug to cure it?

A. Research into the causes of breast cancer is at an all-time high. There is no immediate expectation of a drug that will cure it, but advances in drugs that improve the immune system may hasten a cure for breast and other cancers. Mrs. Reagan's contribution, however, has been to alert women that they can prevent possible death from breast cancer by having a mammogram. What her husband can do is to see that all women, regardless of income, have access to a mammography.

Q. I am a healthy person of 38. I have a little trouble sleeping now and then, but I take care of this with camomile tea. Lately, I seem to have spells of sneezing and watery eyes. I live in the city so I know it is not hay fever. I was thinking of taking one of those products advertised to help colds, but I thought I would ask you if any other products would help.

A. The only thing I can suggest is that you stop the camomile tea for a few weeks and see if your sneezing and watery eyes go away. Camomile comes from the same plant family as ragweed.

Q. I have had a bout of running to the bathroom every 15 minutes and the doctor prescribed Gantanol DS. What kind of drug is it?

A. Gantanol DS is a brand name for the sulfa drug, sulfamethoxazole, double strength. It is usually very effective in eliminating urinary infections such as cystitis. If you do not receive relief from your problem in a few days, be sure to call your doctor.

END OF STORY REACHED

STORY 6

FILE NUMBER	254415
PUBLICATION DATE	09/23/87
DAY	WEDNESDAY
NEWSPAPER	(Copyright 1989) CHICAGO SUN-TIMES
EDITION	FIVE STAR SPORTS FINAL
SECTION	SECTION 2, FEATURES
PAGE	37

CREDIT Newsday
EXTRA KEYWORDS birth control; contraception
KEYWORD-HIT

NEW YORK Fear, distrust and misinformation have created a crisis in contraception in the United States, slowing research and stopping introduction of new and safer birth-control methods, an internationally known women's health expert warns.

"We're basically going to hell as far as contraceptives and women's health is concerned," Dr. Elizabeth B. Connell, professor of gynecology and obstetrics at the Emory University School of Medicine in Atlanta, said in a telephone interview.

"American women are being forced to leave the country to obtain contraceptives," she said. "This is already happening with the IUD (intrauterine device). The Copper T Cu 380 A is now available in Canada, the United Kingdom and continental Europe. American women are traveling to these countries to obtain the device."

Connell said population-control experts in those countries are increasingly perplexed at what is happening to birth-control efforts here: "They're just beginning to realize how crazy we are."

Dr. Gerald Zatuchni, director of the Chicago-based national Program for Applied Research on Fertility Regulation and a professor in the department of obstetrics and gyneocology at Northwestern Memorial Hospital, says prospects are bleak.

"I've been involved in all aspects of concept planning and development for 25 years, and I've never been as pessimistic as I have been the last year or so. I don't see any opportunities for any resurgence in interest in developing new methods of birth control over a minimum of 10, probably closer to 20 years. And it won't change just because there may be a new administration in Washington in 1989."

Zatuchni cited a string of factors involved in the loss of interest in research. The magic of the term population explosion has vanished, partly because of successful family planning programs in some developing countries, he said. Lessening population pressure in the United States and preferences for reduced families also are involved.

"Also, we're in a legal situation with new and existing methods of birth control in terms of all the suits that have been filed and won in some instances. The IUD story particularly has been quite detrimental to companies willing to invest any sort of monies in developing new methods."

The length of time and money at risk to develop an FDA-approved drug or device, he said, affect research and development. "From the cost accounting point of view, it just takes too long and too much money at risk for fairly small financial returns.

"Fear of sexually transmitted disease is important. Today condom manufacturers are working three shifts to keep up with the demand, mostly because of the AIDS scare. It has, in general, indicated to those who are interested in contraceptive research and development that methods would have to be developed that would also be as effective as the condom and spermicides in thwarting infection as well as providing birth control. When you ask yourself what method should we develop, it's pretty obvious you come back to the method called condoms.

"The religious/political factor, of course, is another point. I don't mean to lump them together, but they sometimes go hand in hand. Just the other day the pope came down hard again against any method of contraception other than the so-called natural one.

"The present administration in Washington is not only anti-abortion but anti-family planning. This has affected the whole field in terms of interest to come up with improved methods of birth control."

Other experts long involved with birth control echo concern about the field. Dr. Enayat Elahi, medical director of Planned Parenthood in New York City, said: "There is no liability insurance available for new methods of contraception, which are already available

Sweden, is not available here."

Dr. Richard Lincoln, senior vice president of the Alan Guttmacher Institute in New York City, warned during a recent birth-control association's meeting in Washington, D.C.:

'If the 1960s ushered in a contraceptive revolution, then during the 1980s we're experiencing a contraceptive counter-revolution. The IUD has effectively disappeared from the American market. Spermicides - meaning foams, jellies, creams and sponges - may be next.

"Methods that have already been developed and are available elsewhere are not available to Americans. Clinical research using human subjects to develop new methods has virtually been brought to a standstill in this country."

Another population-control researcher, Laurie Liskin at Johns Hopkins University, said American women are being denied access to some of the safest, most effective and convenient birth-control methods.

In contrast to an American woman, Liskin said: "A woman in Indonesia can get one of several types of copper IUDs, which are not available - and never have been available - in this country. She can also get two different types of injectable contraceptives, one that lasts two months, another that lasts three months. Or she can get a contraceptive implant that lasts five years."

In addition, women overseas have ready access to various versions of the contraceptive Pill, spermicidal tablets and ordinary condoms.

In the United States, however, Liskin said, "There is a general lack of availability of reversible, easily accessible methods of birth control."

The situation is particularly ironic, Connell said, because it was the United States that led the world in contraceptive research and development.

"Americans have provided most of the basic scientific data, expertise and manufacturing capability for contraceptive technologies now in use around the world," she said.

But now, she added, "The United States is losing its leadership role in this area - with potentially disastrous consequences for women and men in this country and elsewhere."

Reasons for the dramatic decline in contraceptive research and development - and the unavailability of newer contraceptive methods - include:

Widespread public misunderstanding of the risks and benefits of various birth-control methods, such as newer, highly effective birth control pills and IUDs.

"The public's fears far exceed the real dangers," Connell said. "This is particularly true of the Pill, whose risks have been grossly exaggerated in proportion to its benefits."

The Reagan administration has decimated family-planning efforts because of the link to the ideologically explosive issue of abortion.

"The current administration has refused to fund any international family-planning organizations that offer abortion counseling or referrals along with other forms of birth control," Connell said.

In 1984, for example, "the Reagan administration abruptly terminated 17 years of support for the International Planned Parenthood Federation because it would not renounce its members' rights to carry on abortion-related activities with their own funds.

"The following year, the U.S. Agency for International Development cut $10 million from support for the United Nations fund for population activities because of its program with China."

In mid-August, the agency again withheld funding from the UN program, despite strong objections from congressmen and senators, and from within itself.

In this country, Connell said, "federal funding of basic research - both in government and university labs - has steadily declined over

been a member of the Planned Parenthood executive committee and has been an adviser to the U.S. Agency for International Development.

Reliable birth control, other than condoms, became a reality in 1960 when the U.S. Food and Drug Administration approved the first oral contraceptives. The Pill is almost 100 percent effective in blocking pregnancy, but initially the oral contraceptives made some women more susceptible to blood-clotting problems.

After the chemical composition of the Pill was changed to decrease the amount of estrogen, problems declined dramatically. For most women it is far safer to take the Pill than to continue a pregnancy to term.

"Despite this track record," Connell said, "The use of oral contraceptives has declined. This is largely because the Pill's early risks received a disproportionate share of public attention."

As for IUDs, she said, serious problems caused by the Dalkon Shield have caused their use to decline dramatically. And because of liability problems, the newest and best of the IUDs - the copper T Cu 380 A - "may never be brought to the U.S. market" even though it already has been approved by the FDA.

END OF STORY REACHED

STORY 7

FILE NUMBER	245012
PUBLICATION DATE	07/27/87
DAY	MONDAY
NEWSPAPER	(Copyright 1989) CHICAGO SUN-TIMES
EDITION	FIVE STAR SPORTS FINAL
SECTION	EDITORIAL
PAGE	24
STORY SIZE	38 INCHES
HEADLINE	Pit-bull attacks mustn't be tolerated
BYLINE	Neal Peirce
SUBJECT	ANIMALS;
EXTRA KEYWORDS	dogs; pit bull
KEYWORD-HIT	

A pit bull named Gadhafi goes berserk at the sight of another dog, strains at its leash, bites its own tongue, sprays saliva and blood. Another pit bull is so keen to attack it tries to chew its way through a chain-link fence. And a street dude named Eric tells about the litter of eight young pit bulls he's raising. Only 8 weeks old, they're already - literally - at each other's throats.

When my photographer colleague Shepard Sherbell came back from Baltimore's Liberty Hill neighborhood with those reports recently, I decided this was one urban story I was happy to learn of secondhand.

But what of the pit bulls? Can this summer's wave of horror stories be passed off as media hype? Hardly. Pit bulls have inflicted 21 of the nation's 29 fatal canine attacks since 1983. Fourteen of the victims have been children under 6 years of age. Each story of a mutilated youngster's body, torn by the vice-like jaws that close with 1,800 pounds of pressure, ripping off flesh with sure intent to kill, is more appalling than the last. And for each fatality, there are dozens of other pit-bull attacks that leave victims with lifetime scars, physical and psychological.

This wave of terror stalking American streets can only worsen. There's an explosion of pit-bull breeding in ghettoes and barrios where idle, embittered youth have chosen the animals as "macho" status symbols, to fight and wager on. In Philadelphia, the pit-bull count has soared from 25 to 4,000 in five years. Time magazine reports the animals are often fed gunpowder or hot sauces to make them mean, live kittens to sharpen their taste for blood.

Dogfighting is a felony in 36 states. But the husky pit bulls

Tab 68

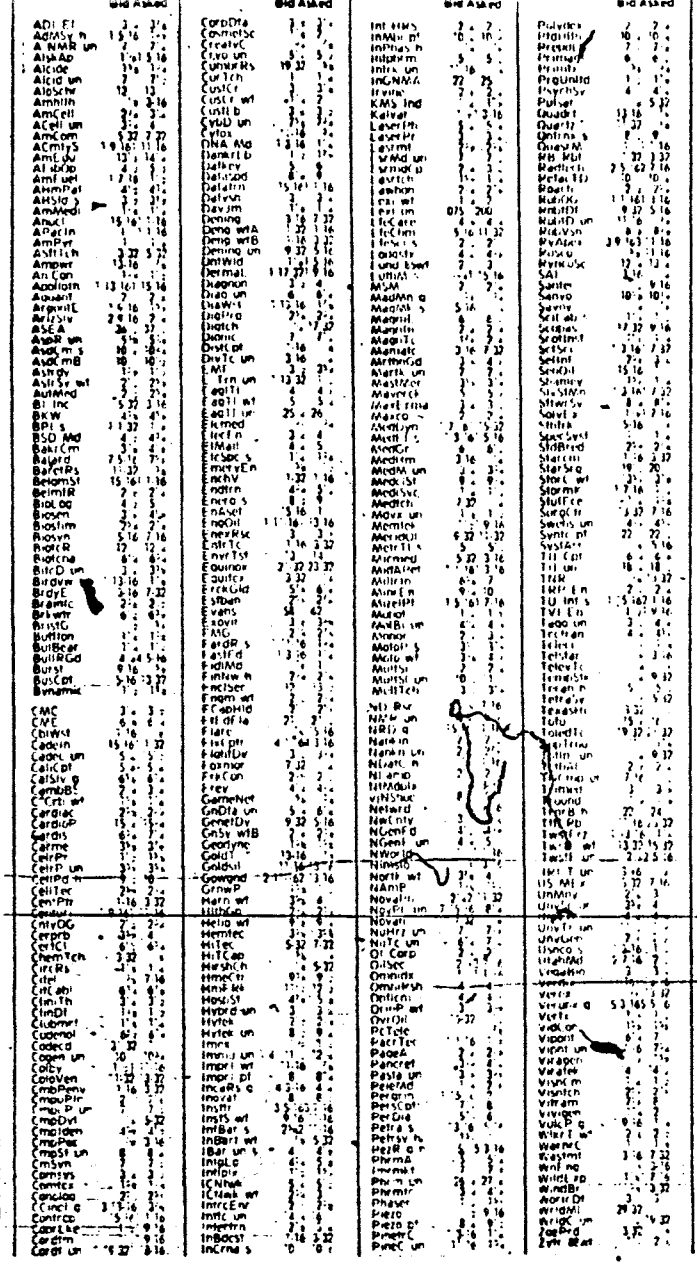
leading us to concentrate on expanding our beauty, health care and direct mail businesses."

At one time, Avon planned as many as 15 Tiffany stores around the country. But Deepak Raj, an analyst at [illegible] 1977, Tiffany had operating margins of a healthy 14 percent, last year they dropped to closer to 3 percent.

In trading on the New York Stock exchange yesterday, Avon stock rose 62½ cents, to $20.875.

Nasdaq Supplemental O-T-C

TUESDAY, JUNE 19, 1984



Kodak Microfilm

ROCHESTER, June 19 (AP) — The Eastman Kodak Company introduced a high-speed microfilmer and a retrieval terminal capable of finding one microfilm image from among 10,000 or more in seconds. Kodak also introduced two packaged information systems — the high-volume KAR-4400 and the low-volume KAR-2200 — which include the microfilm equipment as well as printers, a computer and software. The company said the products are a step toward its goal of creating a system that would allow users to electronically scan images on microfilm and transmit them in the form of computer data. The new products include the R-liant 2000 microfilmer, which Kodak said would cost about $19,000.

Small Bank Closed

JEFFERSON CITY, Mo., June 19 (AP) — The Republic Bank of Kansas City has been closed because of poor lending practices and other problems that rendered it insolvent, Missouri's Commissioner of Finance, Kenneth Littlefield, said. An examination last month by the Federal Deposit Insurance Corporation indicated that the bank had suffered heavy loan losses and had violated banking laws, he said. The bank, which had two offices in Kansas City, reported about $38 million in deposits and $41 million in assets at the end of March.

Massey Layoffs

PARIS, June 19 (Reuters) — Massey-Ferguson Ltd. said it planned to close its harvester plant in Marquette in northern France and lay off all of the plant's 1,430 employees for a least three months because of abnormally high stocks. Production at the plant is forecast to fall to 415 harvesters this year, from 620 in 1983. A spokesman said an annual level of 1,200 was needed to maintain the current work force.

Changes at I.B.M.

The International Business Machines Corporation said a variety of graphics capabilities previously available on its larger computers would be offered for its System/38. I.B.M. also said that terminals used with its intermediate and large systems could now be attached to System/38 by remote communications lines.

[illegible] Securities and Exchange Commission that it is talking with the Amrep Corporation about the repurchase of Amrep stock. The Unicorp group holds 823,337 Amrep shares, or 21.9 percent of the total outstanding.

Unicorp owns and manages real estate investments. Amrep is engaged in land development and residential construction. Both are based in New York. On the New York Stock Exchange today, Amrep was the biggest percentage loser, plunging $3.75, to $19.25.

Sallie Mae Charter

WASHINGTON, June 19 (Reuters) — The Student Loan Marketing Association, also known as Sallie Mae, said it had submitted an application to charter a bank in North Carolina. It said that First Capital Bank, to be based in Raleigh, would specialize in investment and liability products related to education credit, but would also offer limited banking services to the community. Sallie Mae, a federally chartered, stockholder-owned corporation, is a financial intermediary serving the education credit market. By buying insured student loans and providing other financial services to financial and educational institutions and state student loan agencies, it replenishes local supplies of student credit.

Wyeth Vaccine

The American Home Products Corporation said its Wyeth Laboratories Division had ceased production of pertussis vaccine, used to immunize children against whooping cough, because of possible liability problems associated with the shots. A company spokesman said the vaccine had been withdrawn because of higher insurance costs and the risk of liability in lawsuits from users of the vaccine, as well as the cost of defending any lawsuits. Wyeth is estimated to have accounted for 25 percent of the product in the domestic market. Lederle Laboratories is the other major producer in the United States.

Military Contracts

WASHINGTON, June 19 (Reuters) — The Oshkosh Truck Corporation received a $133.4 million Army contract for trucks, the Defense Department said. In addition, the Puerto Rico Sun Oil Company was given a $61.4 million contract by the Defense Logistics Agency for fuel, and Sanders Associates Inc. received a $37.4 million Air Force contract for spare parts for countermeasures test equipment.

Tab 69

into the river in that area, including raw sewage.

They also begin to acclimate themselves to the salty ocean water in which they will live as adults, and some venture into the upper bay near the tip of Manhattan.

They go back up river in the spring, and the pattern repeats

Continued on Page C4

Vaccine Liability Threatens Supplies

By PHILIP M. BOFFEY

WASHINGTON

THE nation's major drug companies, some stung by large liability costs, have been dropping out of vaccine production for years and the trend is continuing, raising fears that future supplies may be jeopardized, important research will be neglected and the costs of vaccines may skyrocket.

The latest dropout was Wyeth Laboratories, which announced June 13 that it had ceased production of a vaccine used to immunize children against whooping cough after more than 30 years of producing it. The company cited "dramatic increases in the cost of participating in this market," chiefly due to liability insurance and the costs of litigation. The whooping cough vaccine has the most serious side effects of any of the vaccines now adminstered to virtually all children in the country under state or Federal laws.

The Wyeth defection continued a trend that has been under way for the past decade or two, according to Paul D. Parkman, deputy director of the center for drugs and biologics at the Food and Drug Administration. During the 1960's, Dr. Parkman said, there were eight manufacturers of the combined vaccine that is used to immunize children against diphtheria, whooping cough, and tetanus; now, after Wyeth's withdrawal,

Continued on Page C13

The New York Times / Rick Friedman

Dr. Mark M. Kuchment, above, found that top Soviet researcher was Alfred Sarant, right.

How a Soviet S Was Finally Pi

By WILLIAM J. BROAD

ABOUT three years ago a kind of obsession began to take hold of Dr. Mark M. Kuchment, a 48-year-old science historian who emigrated to this country in 1975 from the Soviet Union.

While interviewing Soviet émigrés for a Harvard University research project, Dr. Kuchment kept hearing stories of an American engineer who had achieved dazzling success in the secret world of Soviet military research. An American? How could that be?

Dr. Kuchment, who was born in the Ukrainian port city of Odessa and educated in Russia,

Sleuth lear scientist ar American

set out to find the a ultimately solve a ternational intrigu and Federal agents

The tale pieced u nally revealed that a high official in th military research American engineer after the arrest of senberg in 1950, we

Dr. Kuchment, versity and is a fell Center at Harvar work in a recent int shed little light on innocence of Julius were executed in 1 passing atomic bo Union.

But he believes about Soviet techno Soviet officials in e eigner and about th a defector who took

"It's a strange a Dr. David Hollow University on the

Conti

JAZZ: Various artists show talents at festival, page C15./ **THEATER:** Arctic 'Anti

BOOKS: 'The Only Problem' by Muriel Spark, page C17./ **TV:** The making of 'Jes

Vaccine Liability

Continued From Page C1

there are two, Lederle Laboratories of Wayne, N.J., and Connaught Laboratories Inc. of Swiftwater, Pa.

Four other vaccines that are administered to virtually all children are now produced by a single domestic manufacturer, according to Dr. Parkman. The live-virus measles vaccine, made by six companies in the 1960's, and the German measles vaccine, made by three companies then, are now manufactured only by Merck Sharpe & Dohme of West Point, Pa. So is the mumps vaccine, which Merck Sharpe has produced alone for two decades.

The live-virus polio vaccine, which had three makers in the 1960's, is now made only by Lederle Laboratories. And the influenza vaccines, administered on a voluntary basis to millions of adults and children, are produced by only three companies, down from seven in the 1960's.

High Costs of Liability

The reasons for the shrinkage are complex and vary from company to company, according to industry sources and Government officials. Some companies concluded that the vaccine market was too small and profit margins too low. Others dropped out because competitors developed superior products. Still others were squeezed out because the very success of vaccinations in reducing disease also reduced the demand for some vaccines.

But increasingly manufacturers are blaming the high cost of protecting themselves against liability claims by the small number of people who are inevitably harmed by severe adverse reactions to the vaccines. Even if a vaccine is produced with the utmost care in accord with the most stringent specifications, it is virtually certain to cause harm to a tiny fraction of those who use it, or sometimes to those who come into close contact with those who receive it.

Some victims who suffer debilitating physical damage, or even death, receive little compensation for it. They are the unfortunate victims of programs designed to protect the public health. But other victims are successful in winning large liability awards that can eat into the profits of the manufacturers, either through the awards themselves or through legal fees and higher insurance costs.

A report submitted to a Congressional committee this year cited 11 recent court awards or settlements in which victims won between $150,000 and $5.5 million. Sometimes the manufacturers end up paying substantial awards even though they made their vaccines perfectly.

Federal Intervention Sought

The steady withdrawal of vaccine manufacturers has caused alarm among professional organizations and in Congress. The American Medical Association at its annual meeting last week approved a report calling for the Federal Government to assume responsibility for compensating the victims of mandatory childhood immunization programs, relieving the manufacturers of liability risk unless they are negligent.

"Not all of th...

GOING OUT Guide

WHALING WALLS

Long before men ran out West in search of gold and glory, they ran off to sea in search of whales and wealth. That era, 1820 to 1850, when whalers sailed from the Eastern Seaboard, brought with it, most incidentally, its works of art.

The flavor of this period is on the walls and floor of the Museum of American Folk Art, ensconced now in a new home, a building once occupied by John D. Rockefeller, at 125 West 55th Street (581-2474). The show of 65 objects is called "Cross Currents: Faces, Figureheads and Scrimshaw Fancies."

In it are the works of three artists, not household names, who painted families prominent in shipping from Massachusetts to Long Island. Isaac Sheffield worked in New York and Connecticut, painting portraits and miniatures of captains, their wives and children. Orlando Hand Bears of Sag Harbor did the same in the same area. The third is Frederick Mayhewm, whose "naive" portraits have been popping up for years in Martha's Vineyard and New Bedford.

The show includes those essential art pieces of old-time shipping under sail, figureheads. There are also many examples of the carving art called scrimshaw, among them a whalebone piece engraved with a scene of New Bedford, canes inlaid with ivory, jagging wheels of whale ivory.

Open Tuesdays from 10:30 A.M. to 8 P.M., other nights (except Mondays), to 5:30 P.M. Admission: $2; students and over-65's, $1; under-12's, free.

Detail from 19th-century oil painting by Orlando Hand Bears, included in display on the sea at the Museum of American Folk Art.

AL FRESCO

During summer, Al Fresco is New York's great impresario of music, as big as all outdoors. Al fresco concerts fill streets, parks and plazas. Some concerts are formally programmed; others are not only al fresco, but ad hoc.

One of the more popular outdoor concert locations is Bell Plaza, the block-through court of the New York Telephone building, on the Avenue of the Americas, between 41st and 42d Streets. Often, late in the day, a first-rate big band lets loose its jazz here in an unofficial gig. And during the summer, the telephone people sponsor outdoor events, as they will do, starting today, every Tuesday from noon to 2 P.M.

This is the fifth annual Summer Arts Festival, and each week two different musical acts will hold the pavement. Today's stars are Neighborhood Juke Box, a rockabilly band evoking the 1950's sound, and the Tomov Yugoslav Folk Ensemble.

Admission is free. Information: 395-2357.

JAZZ

Joe Barone and Lilyann Carol and their trio have been going, if not steady, at least occasionally, with Jimmy Weston's, the restaurant-club at 131 East 54th Street (838-8384). Mr. Barone plays saxophone and his wife, Miss Carol, is vocalist. Miss Carol was a featured vocalist in the early 1940's with the Louis Prima Orchestra before Keely Smith entered the scene. Mr. Barone performed with Cab Calloway, Jerry Vale and Steve Lawrence.

John S. Wilson visited them at an earlier Weston's engagement and wrote in The New York Times: "The kind of intense, rhythmic and raunchy lounge act that Louis Prima created in Las Vegas is being carried on with some degree of legitimacy by Lilyann Carol and Joe Barone. While their versatile three-man band keeps a shuffle rhythm going behind them, one song flows into another with a smoothness that belies the seeming anarchy of their performance."

Through June 30, they appear daily, except Sundays, from 8 P.M. to 3 A.M. There is an $8 cover and no minimum. Drinks, $4 up. Main courses: $11 to $19.

REVIVAL

In January 1958, Samuel Beckett's second play, "Endgame," had its American premiere at the Cherry Lane Theater, directed by the late Alan Schneider, and it has been a theater perennial ever since then, receiving prestigious and other revivals by companies large and small. Now it is getting a special revival at Theater Row's Samuel Beckett Theater, 410 West 42d Street, where the director is Alvin Epstein, who was in that first performance and appears also in this one, although in a different role.

Brooks Atkinson, in a 1958 review in The New York Times, called it impressive and wrote: "Mr. Beckett is wise in choosing the form of the myth in which to sound his tocsin on the condition of human society. Since his theme is unearthly, the unearthly form becomes it."

In this production, Mr. Epstein is joined onstage by Peter Evans, Alice Drummond and James Greene. Tuesdays through Saturdays at 8 P.M., Also Saturdays at 2:30 and Sundays at 3 and 7. Admission today and tomorrow, before opening on Thursday: $15; after that, $20 and $22. Reservations: 594-2826.

• • •

Tuesday Sports is on page A22.

Richard F. Shepard

Entertainment Events

Music

ENGLISH NATIONAL OPERA, Verdi's "Rigoletto," Metropolitan Opera House, 8.
METROPOLITAN OPERA IN THE PARKS, Verdi's "Ernani," Great Lawn, Central Park, 8:30; rain date, Thursday.
MILLER TIME CONCERTS ON THE PIER: KING CRIMSON, with Adrian Belew, Robert Fripp, Tony Levin and Bill Bruford, Pier at 45th Street and 12th Avenue, 7:30.
NEW YORK CHORAL SOCIETY SUMMER SING, Amy Kaiser, conductor, Cami Hall, 165 West 57th Street, 7:30.
STEPHEN HAMMER, Baroque oboe, Grace and St. Paul's Church, 123 West 71st Street, 8.
AMERICAN NEW MUSIC CONSORTIUM, N.Y.U. Loeb Student Center, Top of the Park, 566 La Guardia Place: Electro-Acoustic Music From the Netherlands, 6; Edward Lewis, trumpeter, and Jack Kreiselman, clarinetist, 7.
BILLY JOEL, rock concert, Madison Square Garden, 8.
MARGARET LENG TAN, pianist, Whitney Museum of American Art at Philip Morris Building, Park Avenue and 42d Street, 8.
AN EVENING WITH THE STARS, Alliance of Latin Artistes Society, Institute of International Education, 809 United Nations Plaza, 8.
ERROL PARKER TENTET, jazz, Grace Plaza, 43d Street and the Avenue of the Americas, 12:15.
JOSE ENRIQUE AYARRA JARNE, organist, Trinity Church, Broadway at Wall Street, 12:45.
CALLE/STADA/STRASSE, classical and dance music, Trinity Church courtyard, Broadway at Wall Street, 1:30.

Dance

RACHEL LAMPERT AND DANCERS, Bessie Schonberg Theater, 219 West 19th Street, 8.
THE ROD RODGERS DANCE COMPANY, Chase Manhattan Plaza, Liberty and Nassau Streets, noon.
NEW YORK INTERNATIONAL BALLET COMPETITION, City Center, 131 West 55th Street, 7:30.

Cabaret

SWEETWATERS, 170 Amsterdam Avenue, Carmen Lundy, singer, 9 and 11.
CAROLINE'S, 332 Eighth Avenue, Gilbert Gottfried, comedian, 8:30.
DUPLEX, 55 Grove Street, Lisa Hunt, singer, 10.
LONE STAR, 61 Fifth Avenue, at 13th Street, John Lee Hooker, country.

Bridge: High Winds in Vermont Get Players Away From Table

By ALAN TRUSCOTT

High winds are a nuisance to athletes, golfers and tennis players, but they rarely affect bridge games. They did so Sunday, however, at a ...

ble when the diagramed deal occurred at the table. North's negative double, suggesting some values outside ...

NORTH
♠ J 7 6 4
♡ 4
◊ 7 3 2
♣ A 7 6 5 2

WEST
♠ K Q
♡ A K Q 8 2
◊ 10 9 8 4
♣ K 10

EAST
♠ A 10 9 8 3 2
♡ J 10 9 6 3
◊ —
♣ 9 3

Federal Intervention Sought

The steady withdrawal of vaccine manufacturers has caused alarm among professional organizations and in Congress. The American Medical Association at its annual meeting last week approved a report calling for the Federal Government to assume responsibility for compensating the victims of mandatory childhood immunization programs, relieving the manufacturers of liability risk unless they are negligent.

"Of all of the armaments of medicine, vaccines offer the greatest potential benefit to the greatest number of persons," the A.M.A. report said.

As examples, the report estimated that one in every 312,500 doses of whooping cough vaccine, and one in every one million doses of measles vaccine would cause brain damage, and that one in every 3.2 million doses of polio vaccine would cause paralysis, mostly in unvaccinated adults who came into contact with vaccinated children.

The Institute of Medicine of the National Academy of Sciences is conducting a study of the factors that are driving companies out of vaccine production and interfering with the development of new vaccines. Roy Widdus, the staff officer for the study, said it was motivated in large part by indications that "the industry which was responsible for producing vaccines was not healthy" and that "people were dropping out" at the very time that advances in biotechnology showed "an enormous potential for developing new vaccines."

Thus far the shrinking vaccine capability has caused no major supply problems. "We don't yet have a crisis, but it may be that a crisis is waiting to happen," said Kenneth Bart, a vaccine authority at the Centers for Disease Control in Atlanta, a Federal agency that purchases vaccines for many of the state childhood immunization programs.

The chief worry is that in cases where there is only a single manufacturer of a vaccine, the supply could be disrupted by an unexpected manufacturing problem, a bad batch of vaccine, a strike by employees or a decision by the last manufacturer to abandon the market.

Another concern is that prices will rise as the number of competing companies dwindles and liability costs continue upward. The price of the combined diphtheria, whooping cough and tetanus vaccine has soared from an average of 11 cents a dose 18 months ago to an average of 99 cents a dose.

The final worry is that research aimed at designing new vaccines will diminish as the number of companies producing vaccines grows smaller.

The Federal Government is trying to head off supply problems by building a stockpile, paid for by the Government and stored at the manufacturing sites.

Meanwhile, Senator Paula Hawkins, Republican of Florida, and Representative Henry A. Waxman, Democrat of California, have introduced legislation that would establish a Federal mechanism for compensating victims injured by vaccines.

Bridge: High Winds in Vermont Get Players Away From Table

By ALAN TRUSCOTT

High winds are a nuisance to athletes, golfers and tennis players, but they rarely affect bridge games. They did so Sunday, however, at a regional tournament in Jeffersonville, Vt.

A tree was blown down and severed a power line. The tennis bubble where the Swiss Teams was being played was deprived of its primary electrical source and began to sway. Rather than rely on the backup system, the management arranged to evacuate the area in the middle of a match.

The evacuation was well executed and entirely orderly, but there was considerable confusion about the tournament, and some players went home.

A Problem for Officials

When play resumed three hours later in crowded substitute playing space, 88 teams had been reduced to 68, and some teams were composed of fragments of original teams. This set a rare problem for officials who have to determine the standings and allocate master points.

The Swiss play was still in the bubble when the diagramed deal occurred at one table. North's negative double, suggesting some values outside hearts, was aggressive.

It encouraged South to persevere in diamonds at the five-level, and East-West went astray. West needed some diamond strength, rather than a wealth of high cards, for a penalty double, and East should have retreated.

West led a top heart and shifted to spades. South ruffed the second spade lead, ruffed his remaining heart in dummy, and drew trumps. The highly favorable club position allowed him to take all the remaining tricks for a score of 550.

East and West were naturally unhappy, and South tactfully refrained from adding to their gloom by pointing out that six hearts was unbeatable with North on lead. Indeed, all 13 tricks can be made if North fails to lead the club ace.

South was happily calculating that his team could win 18 international match points on the deal, and probably win a bundle of victory points in the match. But at that point his small bubble burst although the large one remained intact.

The evacuation was announced, automatically voiding play in the current match. The opponents hurried away, eager to escape from two impending misfortunes, while South stood for a moment, looking mournfully at the table.

NORTH
♠ J 7 6 4
♡ 4
◇ 7 3 2
♣ A 7 6 5 2

WEST
♠ K Q
♡ A K Q 8 2
◇ 10 9 8 4
♣ K 10

EAST
♠ A 10 9 8 3 2
♡ J 10 9 6 3
◇ —
♣ 9 3

SOUTH (D)
♠ 5
♡ 7 5
◇ A K Q J 6 5
♣ Q J 8 4

East and West were vulnerable. The bidding:

South	West	North	East
1 ◇	1 ♡	Dbl.	4 ♡
5 ◇	Dbl.	Pass	Pass
Pass			

West led the heart king.

Chess: Karpov Captures First Place In Oslo Centenary Tourney

By ROBERT BYRNE

The Oslo Centenary Tournament in Norway, celebrating the founding of the city's chess federation in February 1884, was won by Anatoly Karpov of the Soviet Union. The world champion scored 6-3 to surpass by a half-point his nearest rivals, the grandmasters Tony Miles of Britain and Sergei Makarichev of the Soviet Union.

FINAL STANDINGS

Player	W.	L.	D.	Pts.
Karpov	3	0	6	6
Miles	4	1	3	5½
Makarichev	3	1	4	5½
Adorjan	2	0	5	4½
Apicella	1	0	6	4½
de Firmian	2	2	3	4½
Huebner	0	1	6	4
Wedberg	1	2	4	3½
Arnason	0	2	4	3½
Horf	0	3	3	3½

In the sixth round, Karpov and Miles reargued the same Caro-Kann Defense variation they had struggled with in the BBC Tournament in Bath last year. Then Miles won. This time Karpov got his revenge.

In Bath, Karpov had played 9 P-QN4?!, which loosened his position and thus gave Miles the impetus for a sharp counterattack with 9 ... P-K4! Now he offered a positional gambit with 9 B-Q3!?

Miles accepted the challenge with 10 ... QxNP but soon changed his mind and arranged to give back the pawn to catch up in development with 12 ... N-N3 and 13 ... B-R3. However, in the even material position that arose after 15 RxP, Black's doubled KBP's would prove to be a positional liability.

After 20 R-Q7, Miles could have played 20 ... RxP; 21 QxR, QxR; 22 QxP, but it would not have been a panacea since White would still have been able to operate with the threat of P-Q5, which would have a powerful disruptive effect on the black position.

Just as Miles set his sights on a pawn with 22 ... Q-N6 (maybe the defensive 22 ... R-R2 was better), Karpov sacrificed another one with 23 P-Q5!? Now, 23 ... BPxP; 24 RxKP!, QxP (24 ... PxR?; 25 QxPmate); 25 QxQ, RxQ; 26 R/6-K7, R-Q6; 27 N-R4 would give White winning chances for the sacrificed pawn.

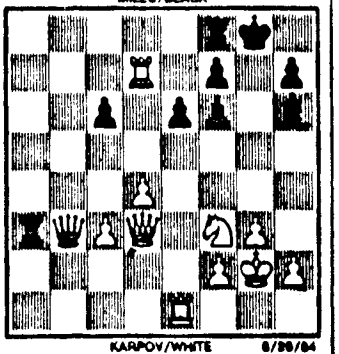
Miles's alternative, 23 ... KPxP; 24 Q-B5, QxP also did not shake off the pressure after 25 R/1-K7, threatening 26 N-K5!.

Miles had indeed insured his king by getting the queens off at move 27, but in the mutual time-scramble that ensued, he lost one pawn after another.

Karpov's 34 N-N5 gave the Englishman no time for 34 ... R-QB6? in view of 35 R-Q8ch, B-B1; 36 N-K6, winning a piece.

Since Karpov's 38 N-B3 forced the win of Black's last pawn (38 ... R-K5?; 39 R-Q8ch, K-R2; 40 N-N5ch picks up a rook), Miles gave up.

MILES/BLACK



KARPOV/WHITE 6/30/84

Position after 22 ... Q-N6

CARO-KANN DEFENSE

White Karpov	Black Miles	White Karpov	Black Miles
1 P-K4	P-QB3	20 R-Q7	R-K3
2 P-Q4	P-Q4	21 R-R8/1	B-R3
3 N-Q2	PxP	22 R-K1	Q-N6
4 NxP	N-B3	23 P-Q5	KPxP
5 NxNch	NPxN	24 Q-B5	QxP
6 P-QB3	B-B4	25 R/1-K7	Q-Q6
7 N-B3	N-Q2	26 QxBP	Q-N3
8 B-KB4	Q-N3	27 QxQch	KPxQ
9 B-Q3	BxB	28 N-K5	B-N4
10 QxB	QxNP	29 RxBP	RxR
11 O-O	Q-R6	30 NxR	B-B3
12 KR-N1	N-N3	31 N-R6ch	K-R1
13 B-B7	B-R3	32 R-Q6	B-N2
14 BxN	PxB	33 N-B7ch	K-N1
15 RxP	R-R2	34 N-N5	R-R1
16 R/1-N1	O-O	35 RxBP	P-Q6
17 RxNP	QxRP	36 RxP	R-R1
18 P-N3	P-K3	37 R-Q6	R-K1
19 K-N2	R-R6	38 N-B3	Resigns

Tab 70

MAKER OF VACCINE QUITS THE MARKET

Immunity Shots for Whooping Cough Will Now Be Sold by Only One U.S. Company

By STEPHEN ENGELBERG
Special to The New York Times

WASHINGTON, Dec. 11 — Connaught Laboratories Inc. has stopped selling whooping cough vaccine, a company official said today. Health experts said the move would worsen shortages of the vaccine, which is used to protect nearly every infant in the country against the potentially fatal disease.

The company, one of two remaining American manufacturers of the vaccine, said it was withdrawing rather than pay sharply higher rates for liability insurance. Earlier this year, Wyeth Laboratories halted production of whooping cough vaccine, citing high litigation costs.

Lawsuits against manufacturers of all vaccines have risen sharply in recent years. Severe reactions are rare, but whooping cough vaccine has been more vulnerable because it causes a relatively higher rate of side effects, including brain damage and death.

Douglas B. Reynolds, a vice president for marketing and sales with Squibb/Connaught Inc., the joint venture company that distributed the vaccine for the Canadian-based Connaught, said the concern's insurers demanded higher premiums and deductibles. "It just wasn't economically feasible to continue production," he said.

Stopped Taking Orders July 1

Mr. Reynolds said the company stopped taking new orders for the vaccine July 1 but was still producing small quantities of the vaccine to fill a handful of contracts expiring early next year. Connaught notified doctors and health officials in a letter last month that its efforts to solve its insurance problems had failed.

Doctors with the American Academy of Pediatrics said that spot shortages had already developed in supplies of the vaccine. The academy has recommended that doctors ration their supplies to assure that the youngest children, who face the worst risk, receive immunization.

Connaught's withdrawal means that each vaccine for childhood diseases, those used to prevent polio, measles, mumps, rubella, diphtheria, tetanus and whooping cough, is now produced by a single manufacturer. The development is likely to stimulate a drive by parents' groups and the drug companies to set up a Federally sponsored system of compensation for children harmed by vaccines.

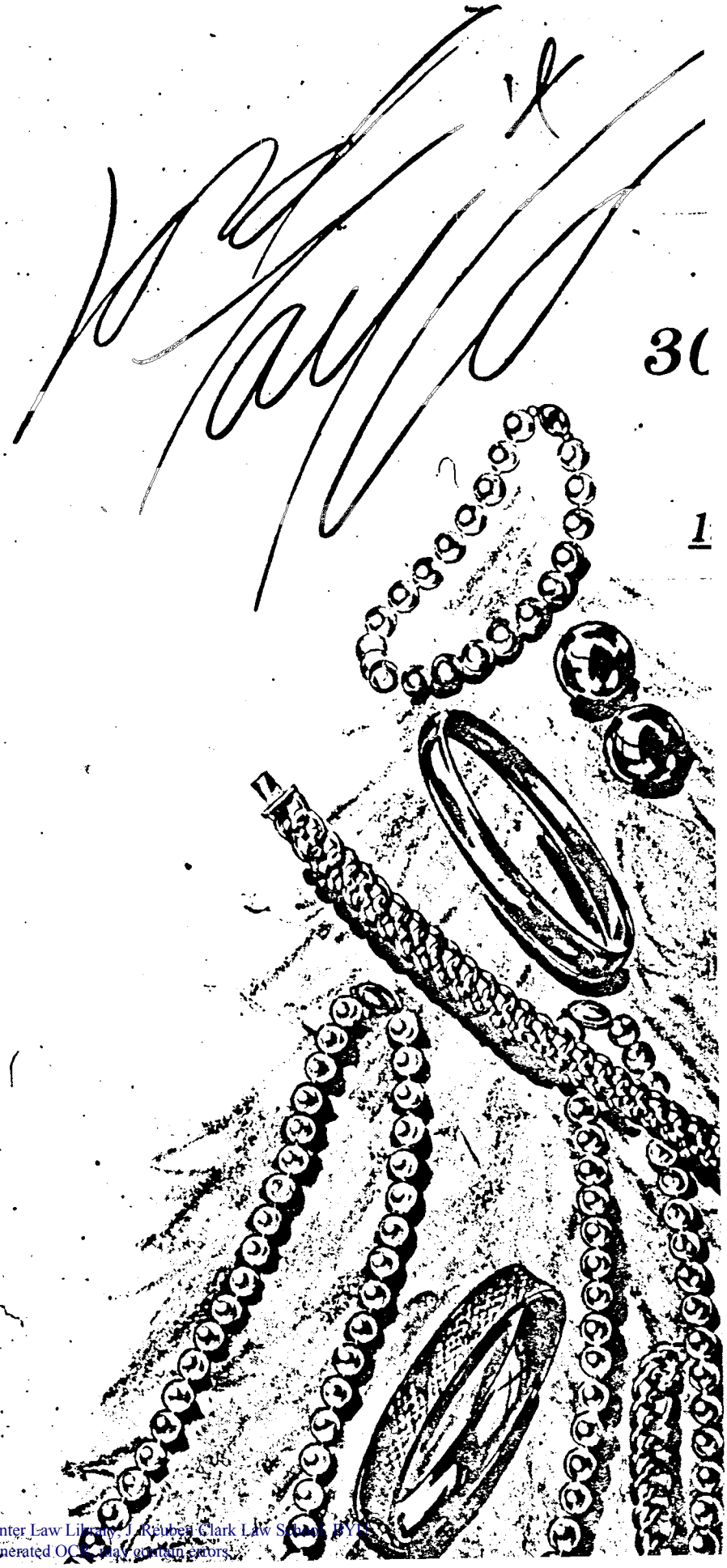
Such a program, financed by a surcharge on each dose of vaccine, could reduce the number of lawsuits, proponents say. A similar bill was introduced in the last session on Congress.

Connaught had held about 25 percent of the market in April 1983 when it raised its price tenfold, to $42 a 15-shot vial. It lost much of its business as a result.

The other remaining producer of whooping cough vaccine, Lederle Laboratories of Wayne, N.J., raised its price in July to $42. It is now expanding to produce the nation's entire supply, said Martha Homma, a company spokesman.

Lederle is also the sole manufacturer of the oral polio immunization.

Dr. Martin Smith, a vice president of Academy of Pediatrics, said that de-



mumps, rubella, diphtheria, tetanus and whooping cough, is now produced by a single manufacturer. The development is likely to stimulate a drive by parents' groups and the drug companies to set up a Federally sponsored system of compensation for children harmed by vaccines.

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Connaught had held about 25 percent of the market in April 1983 when it raised its price tenfold, to $42 a 10-shot vial. It lost much of its business as a result.

The other remaining producer of whooping cough vaccine, Lederle Laboratories of Wayne, N.J., raised its price in July to $42. It is now expanding to produce the nation's entire supply, said Martha Homma, a company spokesman.

Lederle is also the sole manufacturer of the oral polio immunization.

Dr. Martin Smith, a vice president of Academy of Pediatrics, said that dependence on single companies would likely mean a continued rise in the price of all vaccines.

Dr. Smith said reliance on a single manufacturer risked even greater shortages because "it gives us no cushion of safety whatever" in case the plant has to shut for any reason or batches of vaccine are rejected by Federal regulators.

Many of the lawsuits involving vaccine injuries have focused on whooping cough vaccine, which is made from the bacteria that causes the disease, also known as pertussis. It is estimated that 50 to 100 children a year suffer severe reactions, although parent groups contend this figure is understated.

Medical experts say that it is possible for a vaccine to cause a reaction in an otherwise healthy child, even if it is made according to Federal standards and properly administered by the doctor.

New Rules Accelerate Review of New Drugs

WASHINGTON, Dec. 11 (UPI) — Margaret M. Heckler, Secretary of Health and Human Services, announced new regulations today designed to accelerate the review of new drugs and bolster safety monitoring of existing medications.

Mrs. Heckler said the new regulations would cut as much as six months from the time needed to get a new drug on the market, a process which now takes an average of two years or more.

The new rules will allow drugs to be approved based on foreign clinical studies as long as those findings can be substantiated; reduce paperwork up to 70 percent; and allow simultaneous reviews by various offices of the Food and Drug Administration, she said.

Mrs. Heckler said the regulations would also strengthen requirements for reporting by manufacturers and distributors of adverse reactions to medications. Mrs. Heckler's agency oversees the Food and Drug Administration.

Dr. Sidney Wolfe, head of the Health Research Group, a group founded by Ralph Nader, said regulations to accelerate reviews of new drugs could backfire, by reducing the "quality of some reviews" and slowing the drug review process in certain circumstances.

The regulations will be published in the Federal Register this week. Most provisions become effective in three months, with a transition period of up to a year for certain requirements.

Tab 71

Company Offers Vaccine, but Adds Condition

By STEPHEN ENGELBERG
Special to The New York Times

WASHINGTON, Dec. 19 — A major drug company offered today to provide enough whooping cough vaccine to avert a shortage projected for early next year, but only if the Government assumed liability for lawsuits.

Until this year, the company, Connaught Laboratories of Swiftwater, Pa., supplied about 25 percent of the nation's whooping cough vaccine. The company said earlier this month that since July 1 it had been filling only existing contracts because of difficulties in obtaining liability insurance at a reasonable price.

But David J. Williams, vice president and general manager of Connaught, told a hearing of the House Subcommittee on Health and the Environment today that his company had continued production and could deliver three million doses within 60 days if Congress was willing to indemnify it against suits brought by parents of children who suffer adverse reactions.

The chairman of the subcommittee, Representative Henry A. Waxman, Democrat of California, said it was unlikely that Congress would approve such protection. In the Carter Administration, he said, the Government assumed liability for the production of swine flu vaccine and then faced more than $1 billion in claims.

Mr. Williams said Connaught was still negotiating for its own insurance, but he added that it was unlikely to secure new coverage soon.

More Stockpiling Asked

The Connaught offer underscored what Federal officials said at the hearing was the major reason for the shortage of whooping cough vaccine: the increasing number of lawsuits against manufacturers.

At the same time, the head of the Federal Centers for Disease Control, James O. Mason, called for increased stockpiling of vaccine, particularly for whooping cough.

Dr. Mason testified that there were no stocks of whooping cough vaccine on hand and only a three-month supply of the other major inoculations was available.

Dr. Alan Hinman of the disease centers told the committee it would cost about $25 million to buy a six-month supply of whooping cough vaccine at today's prices. He added that the 1985 appropriation to stockpile vaccine for all major childhood diseases was $4 million.

Specialists in pediatric medicine acknowledge that no vaccine is completely safe or completely effective. In the case of whooping cough, an estimated 40 to 50 of the 3.6 million children annually who receive inoculations suffer brain damage.

The American Medical Association and the manufacturers have called on Congress to set up a federally sponsored compensation system that would provide payments but keep the cases out of the courts. This proposal has been opposed by parents' groups.

Postponement Recommended

As a result of the shortage, the disease centers recommended last week that physicians postpone booster shots for infants. Federal officials said this would cause no immediate health problems, but other experts said increased incidence of whooping cough could result if the shots were postponed for a full year.

Dr. Hinman said that if production schedules were met, the country would have adequate supplies of the vaccine by March or April. He said 18 million

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was likely to outst
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REMEMBER

Tab 72

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used; pavulon, a muscle relaxant, and potassium chloride, used for the purpose of halting the heartbeat.

The problem in the execution, however, was not in the choice of drugs, but the mechanical problem of finding a blood vessel free of scars or other damage into which to pass the deadly solution. Mr. Morin's long-term use of drugs had caused extensive damage to blood vessels.

As the lethal injection flowed into his veins, Mr. Morin took a deep breath and then uttered his final words, "Lord Jesus, I commit my soul to you."

The State Attorney General, Jim Mattox, said Mr. Morin "died very calmly."

Another prison spokesman, Charlie Brown, said, "I don't know if it was the longest, but it was the toughest." In five previous executions by injection, the longest it took to insert a needle was 10 minutes.

Mr. Brown said the difficulty in inserting the needles would probably prompt the Texas Department of Corrections to review its procedures for administering the drugs when the condemned person has a history of drug abuse.

Twenty capital punishment opponents held a vigil outside the death chamber and 20 others held a candlelight vigil on the steps of the State Capitol.

Mr. Morin admitted shooting Carrie Marie Scott, 21, outside a San Antonio restaurant on Dec. 11, 1981.

The conviction was upheld by the Texas Court of Criminal Appeals. Mr. Morin never had a stay of execution and his case was never reviewed by a Federal court.

Governor Bars Intervention

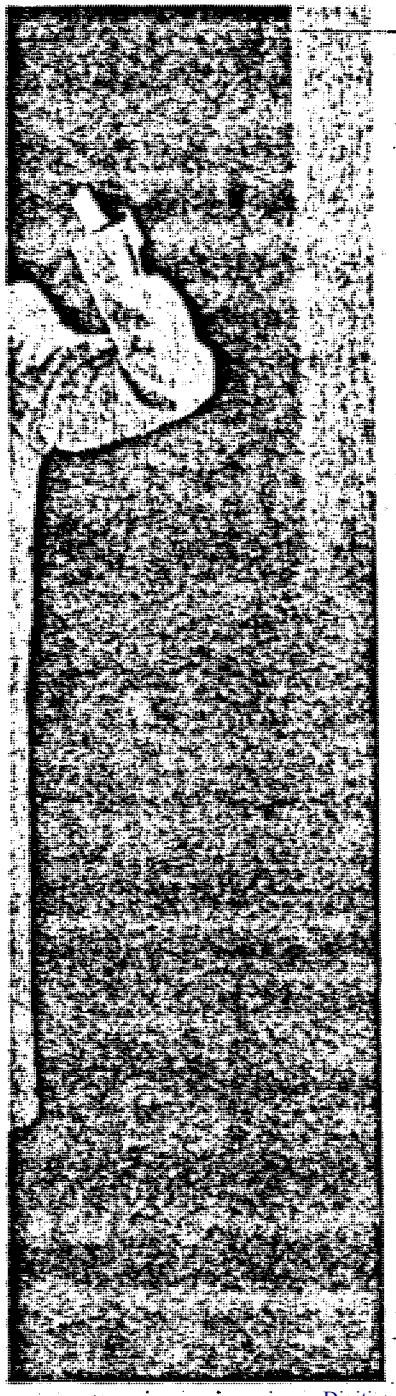
Gov. Mark White, in a brief statement just after 9 P.M. Tuesday, said he would not interfere in the case. District Judge David Berchelmann of San Antonio refused earlier Tuesday to block the execution.

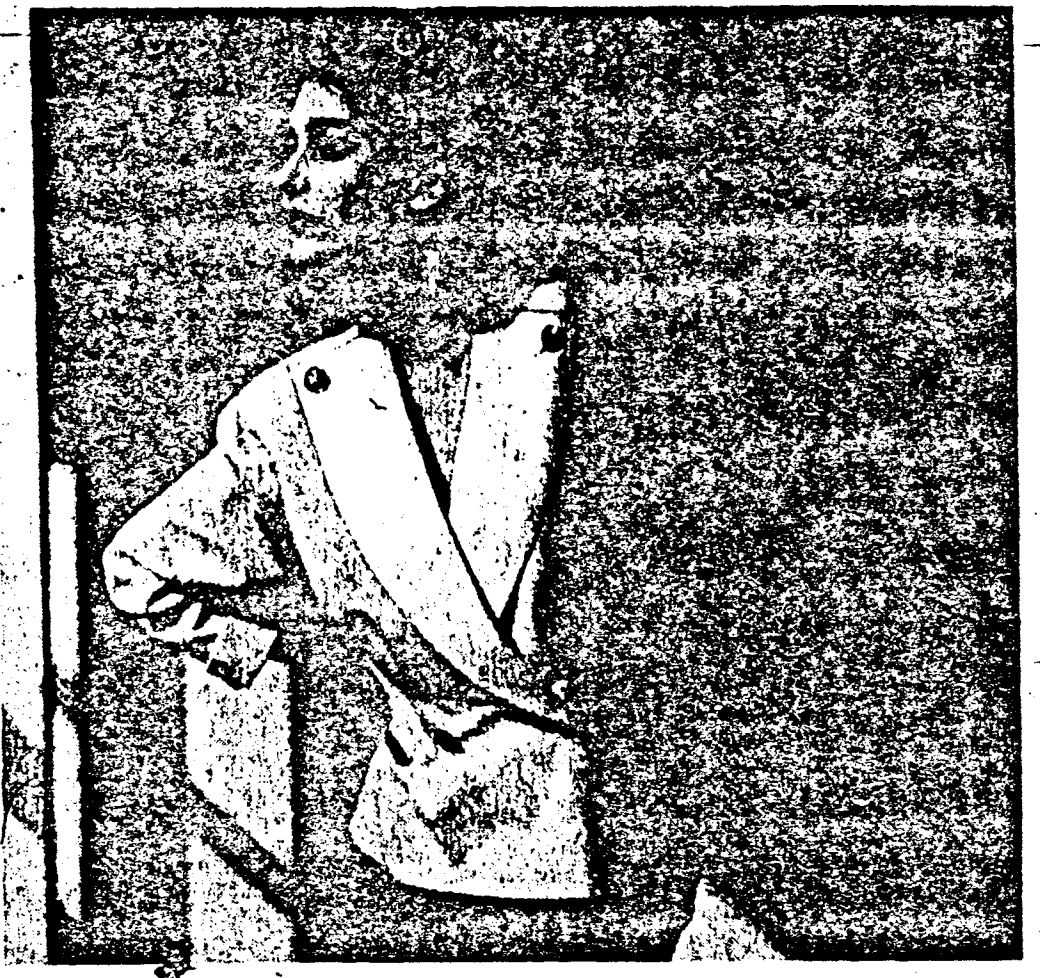
Mr. Morin also faced death sentences for killing Janna Bruce, 21, of Corpus Christi, and Sheila Whalen, 23, whose body was found in the Denver area. Those two slayings and Miss Scott's occurred within a five-week period in 1981. He also was accused of killing two women whose bodies were found in a Utah desert after their abductions from Las Vegas, Nev.

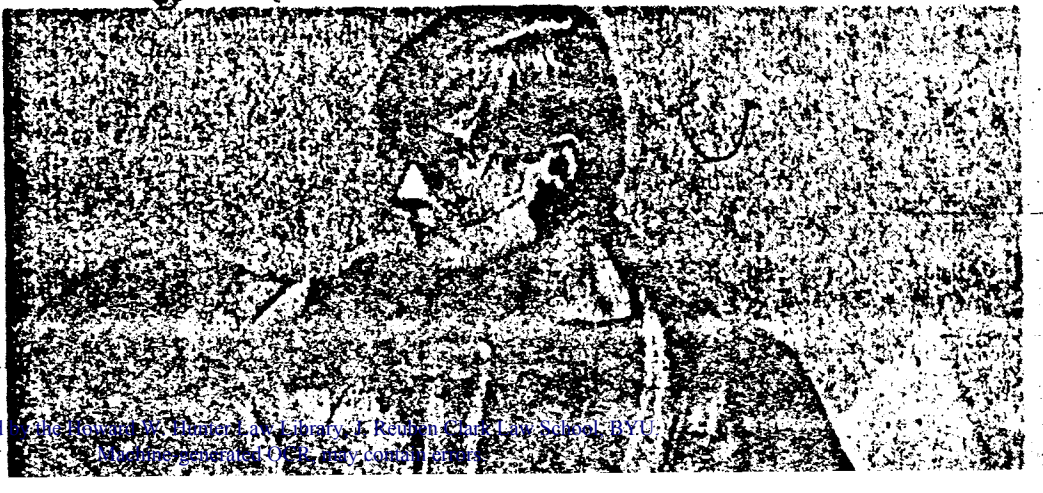
Mr. Morin was the second Texas inmate executed this year, the sixth since the state resumed capital punishment in 1982 and the 40th in the United States since the Supreme Court allowed executions to resume in 1976.

Bendectin Production Ends

CINCINNATI, March 13 (UPI) — Merrell Dow Pharmaceuticals Inc., which won a major liability suit involving the antinausea drug Bendectin, said today that it had abandoned production of the product, which it halted temporarily in 1983. A Federal jury ruled Tuesday that Bendectin, taken by more than 33 million pregnant women, was not responsible for birth defects.







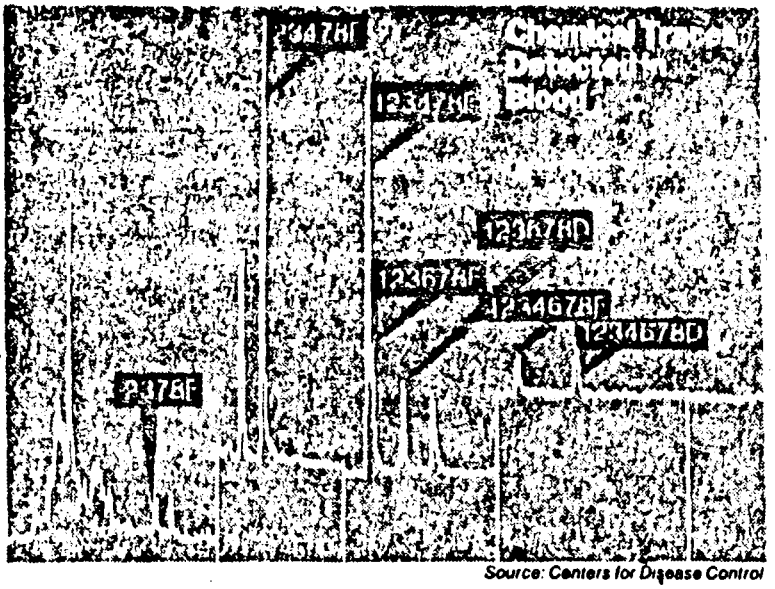
)ma of the Nina

Under square sails on the fore and main masts and ller triangular sails on the mizzen and counter mizzen ts, the crew and passengers ate biscuits, fatback and is seasoned heavily with garlic. They cooked in large cop-kettles over fires kindled with vine shoots and fed with : wood. Stowed below deck were tons of wheat, casks of · and olive oil, cheese, vinegar, salt pork and sardines.
While other recent findings are reviving debate over re Columbus — Admiral Don Christóval de Colón — first ed in the New World on Oct. 12, 1492, the discovery and ysis of shipping documents in the Archive of the Indies in lle are expected to contribute more to the understanding ose early voyages of exploration. How the ships were re-ed and outfitted, how they were rigged, what cargoes they ed and how various contractual arrangements shaped y commerce with the New World are among the many fas-ting details the documents contain.
Of more immediate importance, the knowledge of Niña's ensions and rigging is expected to influence the many rep-; of Columbus's ships that are being planned for the quin-ennial celebration of the 1492 voyage to the New World. ıl now, as the historian Samuel Eliot Morison once wrote no really knew what the Niña, Pinta and Santa María really ed like and every picture of them "is about 50 percent y."
The most striking insights, says Dr. Lyon, who is an ad-t professor of history at the University of Florida, relate to

Continued on Page C3

illness are mired in controversy.
The main object of study so far has been

Continued on Page C5



Source: Centers for Disease Control

Peaks represent dioxins (D) and furans, a class of related chemicals (F). Numbers identify each chemical according to position of chlorine atoms on molecules.

Loss of Drug Relegates Many to Blindness Again

By PHILIP M. BOFFEY

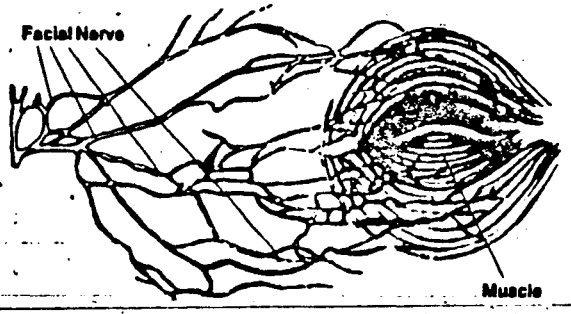
WASHINGTON, Oct. 13 — Thousands of patients with rare neuromuscular disorders are suffering renewed contortions of the eyes, face, neck and other parts of the body because their supply of experimental medicine was cut off when its only manufacturer was unable to obtain liability insurance.

Many who had been faring well are now reverting to functional blindness, unable to read, work, drive or venture outdoors. Others can no longer speak; some suffer debilitating muscle spasms that contort their faces or necks.

Desperate patients are traveling to Canada or England to obtain the experimental drug, made of botulinum toxin. It is the only medicine that gives them satisfactory relief. A few are already resorting to risky, disfiguring surgery as the only alternative to the missing medicine.

At the urging of doctors and patient advocacy groups, roughly 2,000 of the patients have written heart-rending appeals to the Food and Drug Administration and to Congress.

Their problem stems from the fact that there is only one small manufacturer and distributor of the medicine in the United States: Dr. Alan B. Scott, an ophthalmologist who is associate director of the Smith-Kettlewell Eye Research Foundation in San Francisco. In January, Dr. Scott informed some 250 doctors who were administering the toxin in clinical trials involving more than 7,000 patients that he could no longer ship the drug "because of inability to obtain product liability insurance."



Grant's Atlas of Anatomy

Injection of botulism toxin impairs transmission of impulses from facial nerves to eye muscles.

The drug continues to be available in several foreign countries and in a specialized research project at Dr. Scott's laboratory, which can accept only a restricted number of patients.

The researchers testing the drug said they were unaware of other cases in which patients were suffering because a drug had been withdrawn from use as a result of insurance problems.

Over the last six to nine months, as supplies of the drug were gradually used up in this country and as the effects of the last doses wore off in individual patients, the level of desperation has been rising.

"We're in a major bind in the United States right now," said Dr.

Continued on Page C10

ecords 'Me and My Girl,' page C13./ **FILM:** Importing 'Crocodile Dundee,' page C13.

of Theodore Dreiser, page C16./ **TV:** Robin Williams at the Met on HBO, page C18.

Tab 73

Loss of Drug Relegates Many to Blindness Again

Continued From Page C1

Gary E. Borodic, a neuro-ophthmalogist at the Harvard Medical School, who was using the drug to treat scores of patients suffering from involuntary muscle spasms in the eyelids and face. "All my patients are getting worse and worse."

"The patients are just desperate," said Mattie Lou Koster, president of an organization that helps victims of blepharospasm, a disorder in which the eyelids clamp shut involuntarily for periods lasting from a few seconds to several minutes.

The drug, distributed under the name Oculinum, is made from botulinum A toxin, the same deadly substance that poisons improperly canned food. Dr. Scott was a pioneer in developing a therapeutic form of the toxin and supervising its testing in human clinical trials.

The drug is produced in two stages. First, Dr. Edward Schantz, of the University of Wisconsin, cultivates bacteria in the laboratory and extracts the toxin produced by the bacteria. He sends the purified toxin on to Dr. Scott, who uses it to make the drug, which contains only a very tiny amount of the toxin.

Under Dr. Scott's supervision, the drug has been used to treat more than 2,300 victims of blepharospasm and more than 3,300 victims of strabismus, or crossed eyes. It has also been used to treat hundreds of other patients suffering from muscle spasms in the neck, which cause the head to twist and pull sideways; in the vocal cords, which hinders or prevents speech, or in the face, jaw, fingers or limbs.

'Safe' and 'Helpful'

The greatest success has come in treating blepharospasm. The drug is typically injected into the lid and brow, where it paralyzes muscles that cause the eyelids to close. The effect generally lasts a few months, after which a new injection is required. In a paper published last year, Dr. Scott described the treatment as "safe, simple, repeatable, and symptomatically helpful." Neither the toxin nor any other current treatment is directed at the cause of blepharospasm, which is unknown.

Although some eye surgeons say surgery is the most effective treatment for blepharospasm, doctors using the toxin believe the drug is far superior for most patients. Dr. Borodic said 90 to 95 percent of the 130 patients he and colleagues had treated were helped by the drug.

Dr. Jack Wise, assistant professor of ophthalmology at McGill University in Montreal, said he and his colleagues had treated more than 100 blepharospasm patients and roughly 150 strabismus patients with the toxin over the last two years. "Conventional drugs don't work," he said, "and while surgery works, it's mutilating. The surgeons remove muscles from your face or cut nerves. Compare that to an injection that takes 30 seconds and lasts three or four months."

The chief side effects of treatment with the toxin are a drooping of the eyelids, an overflowing of tears and double vision, but all the side effects are transient and minor, Dr. Scott said. In some blepharospasm patients, the drug also interferes a bit with normal blinking of the eyes, forcing the patient to use eye drops.

The disruption of supplies of the toxin has been devastating.

'Back in the Same Condition'

"All my patients have gotten worse, and some have major problems," said Dr. Joseph Jankovic, associate professor of medicine at the Baylor College of Medicine in Houston, who is chairman of the medical advisory board of the organization for blepharospasm patients, the Benign Essential Blepharospasm Research Foundation. He has treated 28 patients for muscle spasms of the eyelids, neck and vocal cords.

"All were very disabled before treatment and now all are back in the same condition," he said. "Many are unable to chew or swallow and two cannot talk."

Mary Sousa, a blepharospasm patient from Somerville, Mass., is bewildered by the problem. "There's fighting about the insurance and other things I don't understand," said Mrs. Sousa, who is 76 years old. She said she used to get five injections of the toxin around each eye every few months, which would allow her to "open my eyes" and "do anything." The only side effect, she said, was that her eyes were black and blue after the injections.

But now, because her last injections in February have long since worn off, "I cannot read anything," she said. "I cannot concentrate on anything. I can't see because my eyes close every second." On bad days, Mrs. Sousa said, she can no longer sew, cook or do housework. "I get mad cooking because it's so hard," she said. "My eyelids are closing down every second. I shake my head to try to get them open."

Some desperate patients are flying to London or Canada to get the drug. Dr. Wise said he and a colleague had treated about 20 Americans in Canada. But Dr. Wise said he did not have enough toxin to treat hundreds or even thousands of Americans who need the medicine, and he added that Dr. Scott had asked the Canadian doctors not to treat vast numbers of Americans, largely because of the liability problems.

"If it's just a few desperate people, that's O.K.," he said. "But not by the busloads. We have no trouble getting the toxin from Scott as long as we do it within reason."

Dr. Scott said his foundation decided to keep sending the toxin to foreign doctors on the assumption that there was less risk of a large damage suit abroad. But he said he was discouraging foreign doctors from treating large numbers of Americans, partly because that might increase the liability risk and partly because the foreign doctors would have difficulty following the progress of American patients for research purposes.

Dr. Scott said there had been no suits or damage claims involving the drug.

'We Stumbled Along'

Many patients and doctors say they are unsure whether the insurance industry is at fault or whether Dr. Scott has somehow failed to solve business problems efficiently or whether the F.D.A. has somehow failed to act expeditiously on Dr. Scott's request for a drug license. All know is that they are unable to get the medication, and no solution appears yet in sight.

> **As supplies of the drug in this country were used up in recent months, the level of desperation rose.**

Dr. Scott said in a telephone interview that his insurance problems began when his research project, which is supported by a grant from the National Institutes of Health, moved from the jurisdiction of one small research institution, the Medical Research Institute of San Francisco, to another, the Smith-Kettlewell Eye Research Foundation, as part of a larger reorganization. In the process, he said, the insurance that previously covered the project was no longer applicable, and he was unable to find another insurance carrier.

"We stumbled along for a month or two," Dr. Scott said, but then Smith-Kettlewell ordered him to stop sending out thousands of vials of toxin because the foundation was unwilling to take the liability risk and feared that continuation of the project would cause its other insurance coverage to be canceled as well. Shipments to other countries were allowed because large damage claims were deemed less likely abroad.

'Bad Name' From Botulism Link

Dr. Scott's efforts to find insurance have thus far been fruitless. He has set up a small company, Oculinum, Inc., to make and distribute the drug in what he describes as a "small-time" operation. "We've tried a large number of insurance brokers and lots of different avenues to insurance companies directly, but nobody is willing to write a policy on it," he said.

One company offered to provide a maximum of $300,000 in coverage, far too little to pay off a large damage claim, for a relatively high premium of $75,000 a year. "That's not much help for a small company," Dr. Scott said.

He noted that the drug, which would have a "relatively small market," had a relatively bad name and apparent high risk" in the minds of some people because of its association with botulism.

Carole Kimball, an account executive with Alexander and Alexander, a large insurance brokerage in San Francisco that has tried to find coverage for Dr. Scott, said his plight was "an example of the liability crisis" in which both insurance companies and those needing insurance are "looking very very carefully" at ways to reduce their exposure to potentially high claims.

Dr. Scott said he was continuing to seek insurance coverage and had also asked the F.D.A. to allow him to charge for the drug so that he could pay for insurance premiums. Ordinarily, the F.D.A. does not allow patients to be charged for experimental drugs whose value has not been firmly proved, but some exceptions have been made.

Dr. Scott's prime goal is to get the drug licensed for regular therapeutic use, a step he said he felt would improve his chances of obtaining insurance. The drug has been in an investigational status for roughly a decade, but Dr. Scott applied for full licensure in April 1985; the F.D.A. is reviewing his data and is expected to issue a license when the review is complete.

"This has been the most frustrating thing I ever worked on," said Abbey Meyers, executive director of the National Organization for Rare Disorders, a Connecticut-based group. "We want the drug to get to patients," she said. "We don't want to see patients suffering like this."

'A Difficult Subject'

Ms. Meyers said she believed that the F.D.A. was "proceeding wisely and as quickly as possible." The agency "finds it a difficult subject and just will not be pressured politically," she said. "Their safety concerns are very valid. It is, after all, a toxin that people die from."

F.D.A. officials declined to comment on the case because of secrecy laws surrounding the handling of drugs under investigation. In a form letter to patients, the agency said: "Although we sympathize with those individuals whose therapy has been interrupted by this occurrence, the Food and Drug Administration does not have the authority to regulate the availability of insurance to cover the use of investigational drugs. We remain willing to work with Dr. Scott regarding the problem of interrupted distribution." The agency also said no license could be issued until Dr. Scott provided proof, as all manufacturers must, that he would be able to make, repeatedly and reliably, a safe and effective product.

Meanwhile, the Medical Research Institute, where Dr. Scott's project was originally based, lost its own liability coverage. Mary Woolley, the executive director, said the institute had been covered for 11 years by the same company and had never submitted a claim or failed to pay a premium, only to be abruptly dropped on Aug. 1. The institute has talked to some 30 insurance underwriters and appealed for help to the California insurance administrator, she said, but the only company that responded set the premium so high that "it was a we-don't-want-your-business quote." The institute's board ultimately decided to keep all research projects going even without insurance.

"I'm very disturbed about this problem because of its implications for research," Ms. Woolley said. "Some wonderful, really qualified people like Alan Scott are going to give up."

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anager's Journal

holics

the past several years, students of ave been bemoaning the declining ivity of the American worker and easing emphasis on family and lei- sults.

wait a minute. Even today, there ople out there—workaholics—who ling to do little else in their lives but

kaholics. It's a word that's handled casually—it was first used in 1971 a front-page item in this very news- and in a book by a professor and or. But exactly who are workahol- what makes them tick?

iding some light is Marilyn Mach- a staff psychologist for New York surance Co., who has just written ould be the first formal study of the t: "Workaholics: Living with Them, g with Them." (Addison-Wesley, 136 cloth $10.95, paper $5.95.)

uldn't have come at a more oppor- me. Paradoxically, scholars suspect e number of workaholics is on the g. As society changes and people be- less sure of their roles in it, more re turn to their work for refuge, ex- Jay Rohrlich, a New York-based alrist who treats workaholics. Addic- work "is the new narcissism," he "You're creating products that are here is a lot of 'I' in work."

ph Hirschowitz, a psychiatrist and te of the Levinson Institute, a Bel- Mass., consulting firm that works

By Liz Roman Gallese

The author is a member of the rnal's Boston bureau.

organizations, adds that as parents more of children, "each generation do more, be more, become more" in to feel satisfied.

all people who work hard are holics. From her interviews with 165 people, Miss Machlowitz identi- nine characteristics of workaholics, make up perhaps no more than 5% of pulation. She says, for example, that holics tend to mix work and leisure, far less sleep than most, and hate nothing.

definition, they constantly work long , far past normal business hours, work weekends. And they bring work on "vacations." If they bother to them at all. A former Nader's Raider works 12 hours a day, seven days a . A pregnant publicist feeling labor rushes back to work from her obste- n's office, after being told that deliv- s hours away. An attorney continues ork in a burning office building until ghters forcibly eject him.

short, workaholics simply can't stop ing. Miss Machlowitz explains that are addicted to work per se, rather to their specific jobs, and that their ction is as much a characteristic of

Medical Costs and the Drug Industry

By Harry Schwartz

Recent developments in this country suggest that medicine and money are becoming more intertwined than ever before. The most spectacular example is the radical change of course by the American Cancer Society with regard to the frequency of cancer detection examinations and the ages at which they should be taken. The ACS is now recommending fewer such tests to be taken at wider intervals because it judges that the benefits its former policy achieved in terms of lives saved, especially the lives of younger adults, did not justify the costs of all those millions of frequent cancer tests.

About the same time it became widely known that the Massachusetts General Hospital has decided against going into the heart transplant business. The reason: a heart transplant requires about eight times the financial and other resources needed for conventional open heart surgery, but the probability of patients benefiting from coronary bypass operations and other such now routine open heart procedures is far greater than the probability of a patient benefiting from a heart transplant.

Non-monetary considerations still seem to play a large role in medicine, of course. When Allard Lowenstein's bullet-riddled body reached a Manhattan hospital emergency room after his shooting some weeks ago, a huge surgical team automatically began a heroic but finally unavailing effort to save his life. Apparently there was no economist there to calculate whether the likely benefits of keeping him alive indefinitely—benefits figured perhaps in terms of the future income taxes he might pay—were worth the hours of determined surgical effort in this case, efforts whose probable hopelessness must have been evident from the beginning.

Medicoeconomic Decisions

But it was clear even before the American Cancer Society policy shift that great pressure exists to use economic criteria in determining medical actions. For years now Americans have been exhorted to realize there is no infinite store of resources to give everybody all the medical care he or she might want. We shall have to decide who may live and who must die in making medicoeconomic decisions, we have been told, and even some Congressmen have been heard criticizing the federal program that pays for kidney dialysis and transplants because it benefits all comers regardless of age, occupation, social usefulness or what have you.

In this atmosphere of growing and forced medical cost consciousness, one might expect that the most cost effective form of medical therapy now available would receive special favoritism. That form, of course, is treatment with pharmaceuticals.

Just the other day, for example, a surgeon reported publicly about the recent sharp decline in stomach and related gastrointestinal surgery. The reason, it turns out, is that a new drug, Tagamet (cimetidine), is so effective against ulcers that many patients who would have been operated on to remove those ulcers in the past are now adequately taken care of by Tagamet prescriptions. The saving, of course, can be reckoned in terms of pain and apprehension avoided as well as of dollars saved in hospital and surgical bills.

A generation ago frequent polio epidemics killed thousands and paralyzed other thousands, leaving to which could survive economically independent and some of even though their respiratory systems had been paralyzed. Today the great majority of American-trained doctors under 40 have never seen a polio case and iron lungs have been relegated to museums of medical technology. We enjoy the fruits of the fantastic effectiveness of the Salk and Sabin polio vaccines, but simply take them for granted.

So similarly do we now take for granted the human and monetary savings of effective antibiotics which have routed most infectious diseases, of the phenothiazines which have revolutionized the treatment of psychotics and permitted many of them to return to the world of work or of L-dopa which has created a new era in the treatment and lives of many victims of Parkinson's disease.

To introduce a new drug in the United States and meet all the Food and Drug Administration requirements now takes on the average about ten years and costs anywhere from $50 million to $60 million.

Yet one need not do much research to discover how adversarial government relations these days are with the pharmaceutical industry, and how little connection exists between the enormous cost effectiveness of many drugs and the treatment the leaders in pharmaceutical research and development receive from Washington.

The adversary relationships have many facets. Perhaps the most important is the fact that to introduce a new drug in the United States and meet all the Food and Drug Administration requirements now takes on the average about ten years and costs anywhere from $50 million to $60 million. Conditions for developing and testing new drugs here are so unpropitious that an increasing amount of pharmaceutical research is being transferred abroad.

Much of the problem arises from the changes in the food and drug laws adopted in the early 1960s in the wake of the thalidomide tragedy. That disaster focused attention properly on problems of drug safety, but the legal changes that resulted focused on tightening the requirements for drug efficacy.

At another level the adversary relationships arise from the anxiety of government to decrease the cost of drugs while excluding consideration of the losses caused elsewhere by this "cheap is better" policy. There can be no doubt of government's burning zeal to promote generic drugs at the cost of brand name drugs, and to introduce price ceilings for generic drugs used in government medical programs.

But apparently few, if any, people involved in this zealous effort ever bother to ask themselves what the long run implications are for pharmaceutical innovation. Why should drug companies invest huge sums in drug research if government policy is so determined to minimize the profits from the successful ventures while ignoring the losses from the many unsuccessful ventures which are inevitable in such probing of the research frontiers?

Finally, of course, there is the whole is-

may be and are assessed against drug firms when, as is inevitable even under the best of circumstances, some people are injured by drug side effects. Moreover, not all of these side effects can be predicted even after the intensive and substantial testing that takes place before a drug can be marketed. Additionally, some American courts are showing a tendency to award damages even when there is considerable doubt that a particular drug or a particular drug company is responsible for the damage at issue.

Thus a Florida jury last March 21 awarded $20,000 to a couple who claimed that their son's birth defects were caused by the morning-sickness drug Bendectin. Bendectin was thus convicted even though it has been taken by 30 million pregnant women, including five million in this country, without any previous serious evidence that it is harmful.

The SmithKline Corporation recently reported that there have been 24 deaths and 383 cases of liver damage among the hundreds of thousands of Americans who have taken Selacryn, an anti-high blood pressure drug that has been taken off the market. There is apparently no confirmed proof yet that Selacryn caused either the deaths or the liver damage, but SmithKline has already felt it prudent to announce that lawsuits may be filed against it, and that the punitive damages asked for in those suits may not be covered by the corporation's insurance. Yet Selacryn has been used widely in other countries without any evidence of the organic damage now said to be occurring here.

DES Lawsuits

The case of diethylstilbesterol (DES) produces the most fear among pharmaceutical manufacturers. It now appears that about one in a thousand daughters of mothers who took DES 20 to 30 years ago may have developed vaginal cancer. Not surprisingly damage suits are being filed, and in some cases awards are being handed down. In one case, a pharmaceutical company was ordered to pay a plaintiff even though there was no evidence that company had produced the DES taken by the plaintiff's mother. It was enough for the court that the company had produced DES.

But if drug manufacturers can be sued successfully for the results following ingestion of their drugs 20 or 30 years ago shouldn't all drugs be tested for 20 to 30 years or longer to make sure they are safe in the long run as well as in the short run?

By such reasoning it would be easy to make a bureaucratic case for simply refusing to let any new drugs be marketed in this country until well into the 21st Century. Yet there is no doubt that drugs are and will continue to be, the most cost effective therapy we have available, while many sick people need better treatments and better drugs for their ailments.

Is it beyond the wit of the American people to produce a better set of arrangements for encouraging the development and marketing of needed drugs—particularly against the most serious illnesses such as cancer—while reaching an agreeable balance between risk and benefit? And shouldn't a government so concerned about the high costs of medical care take another look at its prejudices and preconceptions about the pharmaceutical industry whose products every day make possible vast savings on medical care?

• Mr. Schwartz is a researcher affiliated with the Department of Surgery at Columbia University College of Physicians and

Tab H

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LITIGATION AND INSURANCE

WHEN PRODUCTS TURN INTO LIABILITIES

MICHAEL BRODY

Mr. Brody is an associate editor of Fortune. *From "When Products Turn into Liabilities," by Michael Brody,* Fortune, *March 3, 1986, pages 20–24:*

For the more than two million American women who use intrauterine contraceptive devices, the decision had to have been a shocker. Taking a tack manufacturers in other industries may increasingly be forced to follow, G.D. Searle & Co. announced on January 31 that it would stop selling its Copper 7 and Tatum T intrauterine devices in the U.S., a decision that severely limits a mode of birth control preferred by many women. The reason for Searle's move: product liability lawsuits.

Not that Searle's products were generally considered unsafe. Approved by the U.S. Food and Drug Administration in 1974, the Copper 7 was more frequently prescribed by doctors than the Tatum T. A plastic device shaped like the numeral and partly wrapped with copper wire, the Copper 7 had gained a reputation as "the safest of the IUDs on the market," according to Dr. Louise Tyrer of Planned Parenthood, the nonprofit organization that counsels people on birth control.

Searle had successfully defended the devices in eight lawsuits, three brought against the company by the same attorney. But the lawsuits kept coming, inspired partly by stories of women allegedly rendered sterile by the badly designed Dalkon Shield, an IUD produced by A.H. Robins Co. In two cases in which Searle had argued that its products were not at fault, juries decided against the company. Some 300 suits remain outstanding. At the end of 1985, Searle, recently acquired by Monsanto, discovered it could no longer get insurance to cover its potential liability on the products.

With its U.S. sales of the Copper 7 and Tatum T amounting to only $11 million in 1985, and its legal costs to successfully defend four lawsuits reaching $1.5 million, Searle decided to get out of the business. That leaves only Alza Corp., a small company that sells about 50,000 IUDs in the U.S. annually. A frustrated O. B. Parrish, president of the Searle pharmaceutical division, sums up the result: "We have removed one important option from birth control in the U.S."

While good statistics are hard to come by, virtually all the experts say the number of product liability suits has been climbing sharply, along with the total dollars paid out in damage awards and out-of-court settlements. Figures compiled by Jury Verdict Research Inc. of Solon, Ohio, show that the number of million-dollar jury awards have almost quadrupled over the last five years. The tremendous values some juries have put on victims' lives have helped inflate the awards. Faced with the possibility of costly suits and the certainty of soaring insurance premiums, what are a company's managers to do?

MANAGERIAL RESPONSES

A growing number of corporations appear to be making the choice Searle did—abandoning certain products or deciding not to sell them in the U.S. Other companies, finding that their smaller competitors have bailed out because they can't get insurance, have tried to raise prices to cover their own insurance costs. Frequently, though, they still find themselves up against tough price competition from foreign manufacturers whose cost advantages include lower insurance bills. Companies are bringing lawyers into the process of designing products, documenting and justifying every decision in advance, and plastering the goods they finally turn out with tags and stickers

warning against every conceivable misuse. They are also exploring new ways to settle product liability claims without litigation and pushing for state laws to limit awards, and for federal legislation to revamp product liability law entirely. The chances for success on Capitol Hill are better than ever.

Decisions to file for bankruptcy in recent years by A.H. Robins and Manville Corp., which was hit by billions of dollars in asbestos claims, represent the most drastic managerial responses to product liability claims. However effective bankruptcy ultimately proves as a defense, the extent of the companies' troubles has punched home a sobering lesson. David Holbrook, an executive vice president of Marsh & McLennan, the world's largest insurance brokerage, observes: "Managers throughout the U.S. industry now know that legal liabilities for potentially hazardous products may exceed not only a corporation's insurance but its total assets."

While getting out of a risky line of business may be the right move for a company, how about everybody else? Decisions to bail out have begun to endanger the continued supply of important vaccines, drugs, and medical equipment in the U.S. Consider the example of Bendectin, the only prescription drug available to help pregnant women suffering from severe nausea. In courtroom after courtroom, Bendectin has been found not guilty of causing birth defects; its maker, Merrell Dow Pharmaceuticals, never lost a suit. But publicity given to allegations that the drug was dangerous, together with the specter of the thalidomide disaster of the sixties, kept suits coming by the score. In 1983, confronted with legal bills and insurance premiums that threatened to exceed the product's $13 million a year in revenues—and with devastating potential liabilities if the company lost—Merrell Dow stopped making the drug.

While Bendectin was pulled off the market worldwide, Searle will continue to sell the Copper 7 overseas. Governed by different legal systems and regulations, other countries permit consumers to assume more risk in the U.S. and allow manufacturers to assume less. Yet even the U.S. seems to lack consistency. While women may no longer opt for an IUD, no U.S. court has held a cigarette manufacturer liable for damages claimed by smokers, though the issue is still being hotly contested.

The threat of lawsuits seems to have helped drive several vaccine makers out of the business. Of the companies producing the seven pediatric vaccines that most states require for children entering school, Merck & Co. is the only manufacturer of the combined measles, mumps, and rubella (MMR) vaccine; competitors left the field. The Lederle Laboratories division of American Cyanamid and Connaught Laboratories are the only companies that sell diphtheria, tetanus, and pertussis (DTP) vaccine; and Lederle is the only maker of oral polio vaccine. Lederle's DTP vaccine has gone from $2.80 a dose to $4.29 in the last year, partly to cover increased legal and insurance costs. Wyeth Laboratories ceased selling DTP vaccine in 1984, citing litigation and insurance costs. At least two companies have stopped making polio vaccine.

VACCINE MANUFACTURING

Vaccine manufacturing is a marginal business, even without the threat of lawsuits: the market is small and profits are low. With the baby boom well beyond vaccination age, only three million to four million doses of the MMR vaccine, for example, are sold a year, not enough to support many competitors. The prospect of paying out huge judgments is all companies need to tip the balance against staying in the business. If those that remain were to raise prices enough to cover potential liabilities, the vaccines they make could become prohibitively expensive. In assessing his company's situation, William B. Frellich, Merck's counsel, makes an astonishing statement for a corporate executive. "A good businessman would not be in this business," he says. "The potential liability risk is too high. But Merck is committed to manufacturing vaccines from a social responsibility standpoint."

SKYROCKETING PREMIUMS

Other companies are not willing to shoulder the risk, or can't afford to. Puritan-Bennett of Overland Park, Kansas, a leading U.S. manufacturer of hospital equipment, stopped making anesthesia gas machines in 1984, leaving to two foreign-owned manufacturers a market once shared by half a dozen companies. Even after abandoning the product, C.E.O. Burton A. Dole Jr. says, "Our product liability insurance went up 750 percent this year. We got far less coverage and higher deductibles, so it actually went up 1,500 percent."

In Virginia, William Perry, an engineer, set up a company to design and build hand and foot controls for cars and vans. Perry's son had been crippled in a motorcycle accident, and the father was appalled when he saw the devices available to handicapped drivers. His company has never been sued, but he recently stopped selling his products nonetheless: his liability insurance premiums went up over 1,000 percent in one year. Says Perry, "I would have continued this business even at a loss if I could have got a decent premium."

Big companies can pay big insurance premiums to stay in a business. More than half a dozen companies have given up making foot-

ball helmets in the last ten years. Two names now dominate: Bike Athletic Co., owned by Colgate-Palmolive, and Riddell, part of MacGregor Sporting Goods. Their cost of insurance may exceed manufacturing costs. Says an attorney who defends helmet makers: "The bigger the parent, the better the chances of obtaining insurance. Bike on its own would be virtually uninsurable."

Their staying power might seem to give large companies an opportunity to raise prices once competitors have quit. Not necessarily. In industries as diverse as light aircraft, truck wheel rims, machine tools, and industrial machinery —businesses with long-lived products—U.S. product liability law has given foreign manufacturers the advantage. American manufacturers remain liable for their products as long as they are in use. Having recently entered the U.S. market, foreigners typically do not carry this burden. Piper Aircraft Corp.'s insurance bills, which reflect the risk of lawsuits over any Piper aircraft still flying, amount to $75,000 for every new plane built—more than the cost of manufacturing Piper's smaller planes.

Nor do foreigners carry heavy insurance burdens at home. A recent study by the American Textile Machinery Association found that foreign manufacturers of machine tools and other hardware used in the workplace pay only 1 percent to 5 percent as much for liability insurance in their home markets. In Europe and Japan, employees rely on workers' compensation payments for workplace injuries rather than on suing.

CRISIS IN LIABILITY INSURANCE

"The crisis in liability insurance has made risk management a main concern for top corporate decision-makers," says Robert H. Malott, chairman of FMC Corp. Malott heads the Business Roundtable's task force on product liability. Like other sophisticated corporations, FMC uses "preventive law" programs to reduce the company's exposure to suits. Such programs can include a so-called legal audit of a corporation's businesses, identifying products, services, or manufacturing operations that could trigger lawsuits, and either cleaning them up or scrapping them. The programs also provide for safeguarding product-development documents that could become evidence in a suit. In one case Piper was directed to supply plaintiffs' lawyers with stacks of product-development records. When the company could not find several key papers, the judge prevented Piper from introducing any other evidence; Piper's insurers settled the case for $10 million.

Preventive law also means bringing lawyers in at every step of developing products and improving old ones. Other experts may be called in as well, including specialists like Failure Analysis Associates of Palo Alto, California, a large engineering firm with a huge database on the frequency, severity, and cost of accidents. After identifying the features of a product that have occasioned the most lawsuits, manufacturers can try to improve the product or educate consumers in its proper use. Several years ago manufacturers were hit by a wave of lawsuits over multipiece truck wheel rims, which can explode when huge high-pressure tires are mounted on them. Failure Analysis did statistical and engineering studies that showed the multipiece rims had accident rates no higher than singlepiece rims, and that the real culprit was the procedure that mechanics were using to inflate and mount the tires. The findings led to industry-wide training standards that cut injury rates by 80 percent.

But preventive law can do only so much. No matter how carefully decisions on product design have been documented and justified, it is virtually impossible to prove to a court equipped with 20/20 hindsight that a design could not have been improved upon. Riddell, whose football helmets protect the pros, was recently slapped with a $12-million judgment in the case of a high school football player who broke his neck in a scrimmage. The jury decided the helmet should have carried a sticker warning players of the danger of butting opponents with it. Riddell has appealed the case.

NEW PROCEDURES

The risk and expense inherent in litigation have led a handful of companies to experiment with procedures to try to settle claims before lawsuits are filed. While Union Carbide's efforts in this respect have been overshadowed by the Bhopal disaster, the company's chief litigation counsel, Robert A. Butler, says it has experimented with so-called mini-trials, presided over by a company executive, in product liability cases involving workmen injured by accidental exposure to toxic chemicals. The Center for Public Resources, a New York nonprofit operation financed by over 150 major corporations, has also developed some alternatives to litigation. The center helped set up, for example, the Asbestos Claims Facility, a forum for settling disputes among insurers, manufacturers, and plaintiffs over the payouts on asbestos lawsuits. So far, more than 25,000 claims have been filed.

In the eyes of corporate managers, the chief appeal of private dispute resolution is the prospect of keeping catastrophic injuries from evoking a jury's sympathy—and generosity. One dramatic variation on the idea comes from Professor Jeffrey O'Connell of the University of Virginia Law School. O'Connell has drafted a no-fault insurance program for high school

football players and other student athletes. It has been adopted by two-thirds of the nation's school districts, at a cost to the schools of $1.40 per athlete per year. Under it, if a student is severely injured, the school district offers the family the option of accepting a settlement that will pay all his medical and rehabilitation expenses, and compensate him for his estimated lifetime earnings loss. In exchange the family agrees not to sue. The offer has been accepted by the families of all 24 young athletes seriously injured since the program took effect in 1981. The families may still sue equipment manufacturers, who have not joined the program but are thinking about doing so.

What makes the system work, O'Connell argues, is that families of plaintiffs with truly appalling injuries face enormous expenses and terrifying uncertainty about the future. Because claims against mass-market products—cars, say, or power tools—could swamp the system, it would seem to have the best chance of working for industries whose products are blamed for relatively rare but severe accidents—sports equipment, medical equipment, drugs. By limiting claims to severe injuries and by barring recipients of compensation from also suing manufacturers, the system might avoid the loopholes that have made insurance so expensive in states with no-fault auto plans.

For now, however, most companies have contented themselves with trying to change existing product liability laws at both the state and federal levels. Lawsuits against corporate defendants with deep pockets, Malott argues, "have turned the courts, in effect, into an erratic, backdoor system of nationalized health and accident insurance, financed by corporate insurance premiums." It's time to get a better system, but until one comes along, companies are mostly stuck with hard choices.

Tab 76

Drugs and Health

Economic Issues and Policy Objectives

Edited by Robert B. Helms

American Enterprise Institute for Public Policy Research
Washington and London

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Statements

Yale Brozen

In considering a research agenda for evaluating public policy toward pharmaceuticals, one fact should be kept stage center: drugs are our most cost-effective input in supplying the demand for health. A ten-dollar prescription is frequently a substitute for $2,000 worth of hospital services—a substitute that produces a positive outcome with much higher frequency than hospital care.

There is, at present, a long list of ailments that still require costly and frequently ineffective treatments and for which there is no low-cost drug substitute. Our progress in the past in producing drug substitutes for such procedures and the developments on the horizon indicate that pharmaceutical innovations could contain the cost explosion in the health industry. If we are serious about minimizing costs, our best bet is to increase the number of drug innovations. "It should be clearly recognized that existing drugs are inadequate to deal with most of the diseases we face."[1] I would suggest, then, that the foremost item on any agenda is to learn as much as we can about what factors affect the size and productivity of the pharmaceutical research effort. There is much that can and should be done to increase research productivity, particularly in view of its marked decline since 1962.[2]

Because drugs are cost-effective in producing health, I tend to lose patience when I see so much effort devoted to finding a monopoly explanation for pricing in the drug industry. It has been demonstrated that what some investigators blame on monopoly is usually a disequilibrium phenomenon in a competitive market[3] or a consequence of ar-

[1] William M. Wardell, *Regulation and Drug Development* (Washington, D.C.: American Enterprise Institute, 1975), p. 144.

[2] Henry Grabowski, *Drug Regulation and Innovation* (Washington, D.C.: American Enterprise Institute, 1976), pp. 36, 54. Apparently, productivity of pharmaceutical research is now about one-sixth of what it was before 1962.

[3] Yale Brozen, "The Antitrust Task Force Deconcentration Recommendation," *Journal of Law and Economics*, vol. 13, no. 2 (October 1970), pp. 279–92.

bitrary or governmentally required accounting conventions.[4] If we want to investigate pricing, let us find out why the prices of drugs are so low relative to their value when that value is measured relative to nondrug alternatives. Why is it that drug prices have consistently fallen relative to the consumer price index?

A high-priority item for the research agenda is a measurement of the benefits of drugs. If they are a great bargain, as the evidence so far suggests, we need to make that obvious. We need to revive memories of the day when drugs were referred to as *miracle* drugs. Apparently, the drug industry has fallen to the state of the senator who, after reminding his constituents of the projects he had obtained for his state ten years before, was asked, "So what have you done for us lately?"

The importance of measuring explicitly the value of the medical innovations produced by the drug industry should not be underestimated. My reason for believing this is that attitudes in the making of policy are colored by notions of "me-too" chemical entities, as if research efforts were and are being devoted to reruns that serve no useful purpose. The me-too propaganda has been exposed,[5] but its influence lingers. Policy-making and regulatory attitudes are also colored by notions that the industry can promote any chemicals, no matter how lacking in efficacy, into multimillion-dollar moneymakers by bribing physicians with samples and prizes.[6] It is this sort of attitude that leads some Food and Drug Administration (FDA) officers to demand such absurdities as comparative efficacy studies and to demand repeated efficacy studies to replicate what the efficacy studies have already proved.

Attitudes are also colored by the belief that the drug industry makes so much money that we might as well "stick it to them" by demanding costly efforts, no matter how little the value of duplicative efforts or how much delay is suffered in drug introductions. Commissioner Kennedy, testifying in the 1979 House drug innovation hearings, argued that drug firms are doing magnificently in financial terms and that they can afford to pay for whatever nonsense is demanded by the FDA without stinting on their research effort.[7] It is time that the Kennedys were told

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[4] Kenneth W. Clarkson, *Intangible Capital and Rates of Return* (Washington, D.C.: American Enterprise Institute, 1977); Robert Ayanian, "The Profit Rates and Economic Performance of Drug Firms," and T. R. Stauffer, "Profitability Measures in the Pharmaceutical Industry," in Robert B. Helms, ed., *Drug Development and Marketing* (Washington, D.C.: American Enterprise Institute, 1975).

[5] Larry L. Deutsch, "Research Performance in the Ethical Drug Industry," *Marquette Business Review*, vol. 17 (Fall 1973), pp. 129–43.

[6] S.1075 contains a provision prohibiting promotional gifts to physicians whose value exceeds ten dollars.

[7] U.S. Congress, House, *Drug Innovation Hearings*, 96th Congress, 1st session, June 21, 1979, transcript, p. 46. Cited in American Enterprise Institute Legislative Analysis, *Proposals to Reform Drug Regulation Laws* (Washington, D.C., 1979), p. 37.

that real resources are being consumed in FDA-demanded boondoggles—resources that could be producing lifesaving innovations that are not being produced.

We need to demonstrate just how competitive the drug industry is. A showing of how low drugs are priced relative to their value would help in that endeavor. We also need to demonstrate just how profitable research is—apparently it is no longer very profitable[8]—to end the demand for boondoggles.

Some of the research needed is conceptual rather than empirical. It seems to many economists that drug prices are high relative to marginal cost—which means to them that the industry is not competitive—but their notion of the relationship of price to marginal cost is based on a primitive conception of marginal cost. Professor Telser has demonstrated that marginal cost is a bit more complicated than the usual economist's notion of this concept.[9] His work needs extension and elaboration in language and examples from the pharmaceutical industry that can be comprehended by minds less subtle than his.

While we are clarifying some of the primitive notions we use when introducing innocent students to economics in order to make these notions into operational concepts appropriate for research use, we should also remove some of the obfuscation resulting from the use of the structure-conduct-performance paradigm. Perhaps the boxes are useful, but the arrows from structure to performance point in the wrong direction.[10] Instead of automatically accepting the notion that structure determines conduct, which determines performance, we should recognize that it is performance and conduct that determine structure.[11] The efficient and innovative firm that behaves competitively wins the market. A concentrated structure and a variety of products result from such good performance. Concentration and product variety are a proof of competitive conduct and good performance,[12] not a cause of bad conduct and poor performance.

I would suggest that we apply an upended structure-conduct-per-

[8] Meir Statman, *Returns on Pharmaceutical Research and the Competitive Equilibrium* (Washington, D.C.: American Enterprise Institute, forthcoming); David Schwartzman, *The Expected Return from Pharmaceutical Research: Sources of New Drugs and the Profitability of R&D Investment* (Washington, D.C.: American Enterprise Institute, 1975).

[9] Lester G. Telser, "The Market for Research and Development: Physician Demand and Drug Company Supply," herein.

[10] Yale Brozen, *Industrial Concentration and Public Policy* (New York: Macmillan, forthcoming).

[11] Almarin Phillips, "Structure, Conduct, and Performance—and Performance, Conduct, and Structure?" in J. W. Markham and G. F. Papanek, eds., *Industrial Organization and Economic Development* (Cambridge: Harvard University Press, 1970).

[12] George J. Stigler, appendix to "A Theory of Oligopoly," *Journal of Political Economy*, vol. 72, no. 1 (February 1964), pp. 44–61. Reprinted in Stigler, *The Organization of Industry* (Homewood, Ill.: Richard D. Irwin, 1968), pp. 60–62.

formance paradigm to an analysis of the history of innovation and industrial structure in each of the various therapeutic categories. We need to analyze the benefits of innovations as they appear and the benefits of new product varieties. I believe we would find that we should be praising concentration and product variety, then, as evidence of good performance and competitive conduct. Product "differentiation" is a virtue, not a sin.

On our research agenda, we should also be looking into what proof of efficacy there is of the investigational new drug (IND) requirement and of the proposed monitoring of animal studies. The IND requirement presumably was installed to make sure that animal toxicology studies were adequate and that no harm would be done in human trials. Has the harm done to patients in clinical studies been reduced by the IND requirement? Since practically zero harm was done in clinical studies before the IND requirement was installed, I believe that the efficacy of the requirement is nonexistent. Let us apply the same standards of efficacy to such requirements as the FDA applies to new chemical entities. If the efficacy of the IND requirement cannot be demonstrated, then there are grounds for discarding it—for removing it from the regulation panoply.

Let us also examine the efficacy of the efficacy requirement. There is some evidence indicating that it is not effective.[13] Let us apply the efficacy requirement standard to efficacy demonstration requirements. I think a double-blind test here will demonstrate that there is not even a placebo effect.

The whole regulatory mechanism may be a gigantic sham with enormous costs and no benefits. If it is a charade, we should go about the task of unmasking the charade. If it is not, let us prove it is not. If some parts are valuable and some are not, let us sort them out. It is time to get on with this task, above all others.

William S. Comanor

There are really two literatures on the economics of the pharmaceutical industry. These two literatures focus on different positions and come to different conclusions for public policy. In this comment, I briefly examine both these literatures and how they relate to each other, for it appears that they frequently pass as ships in the night and do not really confront each other on the relevant issues.

The first literature is perhaps the more conventional. It follows the

[13] Sam Peltzman, *Regulation of Pharmaceutical Innovation: The 1962 Amendments* (Washington, D.C.: American Enterprise Institute, 1974).

Tab 77

DRUG LAG

Federal Government Decision Making

RITA RICARDO CAMPBELL, Ph.D.
with a foreword by
WILLIAM M. WARDELL, M.D., Ph.D.

HOOVER INSTITUTION PRESS 1976
STANFORD, CALIFORNIA 94305

Kennedy, Edward. "[Keynote] Address." Press release of speech before the Tulane Medical Symposium on Principles and Techniques of Human Research and Therapeutics, New Orleans, November 2, 1975. Mimeographed.

Rutstein, David P. Statement in U.S. Senate, Select Committee on Small Business, Subcommittee on Monopoly, February 6, 1973. Mimeographed.

Schmidt, Alexander. *The Commissioner's Report of Investigation of Charges.* October 24, 1975. Mimeographed.

———. "Communication as the Basis of Regulation." Food and Drug Law Institute/FDA, December 11, 1973. Mimeographed.

———. "Dimensions of Change in the FDA." Speech before the Pharmaceutical Advertising Seminar, Chicago, September 3, 1973. Mimeographed.

———. "The FDA Today: Critics, Congress, and Consumerism." Speech before the National Press Club, Washington, D.C., October 29, 1974.

———. "The FDA in 1985." Speech before the Tulane Medical Symposium on Principles and Techniques of Human Research and Therapeutics, New Orleans, November 5, 1975. Mimeographed.

———. Statement in U.S. Senate, Judiciary Committee, Subcommittee on Separation of Powers, July 21, 1975. Mimeographed.

———. Statement in U.S. Senate, Committee on Labor and Public Welfare, Subcommittee on Health, August 16, 1974. Mimeographed.

[Schultz, Harold.] "Risk-Benefit Considerations in Food Safety." Attachment A to minutes of November 14-15, 1974, joint meeting of National Advisory Food Committee and National Advisory Veterinary Medicine Committee, November 1974. Mimeographed.

Seidman, David. "Protection and Overprotection, the Politics and Economics of Pharmaceutical Regulation." Paper given at Midwest Political Science Association conference, April 29-May 1, 1976. Mimeographed.

Simmons, Henry. Statement in U.S. Senate, Select Committee on Small Business, Subcommittee on Monopoly, February 5, 1973. Also five addenda (A-E), and exhibits 4-18; and "Status Report on a Number of

Commissioner Schmidt's testimony dated August 16, 1974 stated:

> In sum, it is clear that the rate of drug introduction into the United States has slowed since the 1950's. This slowdown is worldwide, but is somewhat greater in this country than in other advanced countries. There appear to be some drugs unavailable in this country that represent modest but real therapeutic gains. We are concerned about this and want to be very sure that useful drugs are not held back unnecessarily. It also appears that drug research has moved abroad to some extent. We are also concerned about this, because of its negative impact on the development of good clinical investigation in therapeutics and because it will further delay the availability of useful drugs.[73]

And on October 29, 1974, Commissioner Schmidt, in what might be considered a plea for a positive rather than a negative legislative mandate to the FDA, spoke at the National Press Club as follows:

> What I see as a seriously unbalanced and deleterious pressure can be remedied only by Congressional and public recognition that the *failure* to approve an important new drug can be as detrimental to the public health as the approval of a potentially bad drug. It's often forgotten—and sometimes conveniently so—that our responsibility to get good new drugs into medical practice is at least as important as our responsibility to keep worthless or dangerous drugs off the market.[74]

Meanwhile, an improvement in FDA's approvals of NDAs had occurred between 1971 and 1976. In September 1974, Dr. William Wardell, their most effective critic because his criticism was based on primary scientific data and was reported in terms which FDA staff could more easily understand than criticism by economists, had stated before the Senate Subcommittee on Health:

> Over the past 2½ years, a marked improvement has occurred in the rate of FDA approvals of medically useful new drugs, with resulting benefits for the American patient. . . .Large anachronisms still remain—e.g., in the cardiovascular area. . . .Nevertheless, in general the FDA has come to be more in touch with up-to-date standards of medical practice, and has done much to regain the confidence of the scientific and medical communities. . . .[75]

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73. Ibid., p. 28. Although dated August 16, 1974, was referred to September 25, 1974, several times but not actually orally presented during the hearings.

74. Alexander Schmidt, "The FDA Today: Critics, Congress, and Consumerism," speech before the National Press Club, mimeo, p. 12.

75. U.S. Senate, Joint Hearings, op. cit., September 27, 1974, p. 507.

Tab 78

LIABILITY & INSURANCE BULLETIN

The weekly newsletter on liability and insurance for industry, government, and the professions.

Volume 1, Number 14 | BURAFF PUBLICATIONS, INC. | November 3, 1986

Florida Tort, Insurance 'Reform'

INSURERS APPEALING COURT DECISION UPHOLDING MOST PROVISIONS OF NEW LAW

TALLAHASSEE, Fla. — A circuit court ruling upholding all but one of the major provisions of Florida's Tort and Insurance Reform Act of 1986 is being appealed by insurers seeking to take their case to the state Supreme Court.

Leon County Circuit Court Judge Charles E. Miner Jr. ruled Oct. 24 in favor of the state's Department of Insurance, along with fellow defendants Florida Power and Light Co., the Florida Medical Association, and the Florida Railroad Association. A group of 23 insurance companies, three industry groups, and the Academy of Florida Trial Lawyers challenged the law in July, charging that it violates both the state and federal constitutions (*LIB*, July 28, p. 1).

But Miner rejected those claims, throwing out only one aspect of the comprehensive legislation: the refund of premiums on commercial liability policies in force prior to July 1, 1986, the effective date of the law. Such rebates, he said, "substantially impair ... contracts and violate due process rights." The law required rebates on all commercial liability policies in effect between Oct. 1, 1986, and Dec. 31, 1986, no matter when they were written. Insurers testified the provision would have cost them $140 million.

On Oct. 29, the First District

(Continued on p. 2)

Self Insurance

AMENDMENTS ON RISK RETENTION SIGNED INTO LAW BY PRESIDENT REAGAN

Legislation that will ease restrictions for businesses, professional groups, and others seeking to create self insurance pools or buy liability coverage was signed Oct. 27 by President Reagan.

The legislation (S 2129) amends the Product Liability Risk Retention Act of 1981 by expanding coverage to include general liability insurance. It permits self-insurance groups which meet the financial requirements in their chartering states to operate in all 50 states.

The bill also includes language that would permit non-chartering states to require such groups to demonstrate financial responsibility. It provides that a state's authority to impose or apply financial responsibility requirements is subject to statutory prohibition that a state cannot impose any discriminatory requirements on a risk retention group.

Sen. John Danforth (R-Mo) one of the Senate bill's original sponsors, said the measure is not a "complete solution" to the unavailability of insurance, but by creating new alternatives for liability coverage, "it represents an important step toward alleviating the problem." □

Inside ...

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Florida, from p. 1

Court of Appeals in Tallahassee extended to the insurance industry most of the injunctive relief previously granted by the lower court, including a delay of rate filings required by the law and a stay on the payment of special credit refunds. The new extension expires Nov. 7.

Under the injunction issued by Miner some months ago, the insurance companies were ordered to pay the special credits into an escrow account. Under the appeals court's extension, however, no payments must be made. Also under the extension, the insurers are not required to pay $500 to establish the joint underwriting association called for under the new law, although the administrative process for creating the body will continue.

The appeals court also passed the matter directly to the Florida Supreme Court for review. "We expect that the industry is going to ask the Supreme Court to extend injunctions to prevent implementation of the law," Sandra Fish, a public information specialist in the Florida Department of Insurance, told *LIB*. "We're going to vigorously oppose any efforts to keep us from moving along with this law."

The major provisions of the new law were upheld under Miner's ruling, including the requirement, cited as most onerous by insurers, to roll back commercial liability insurance premiums and freeze rates and increases until Jan. 1, 1987.

In other "insurance reform" provisions, the law gives the Department of Insurance greater authority to review and approve property and casualty rates, restricts cancellation of policies, creates a joint underwriting association, creates an excess profits law for property and casualty insurance, and requires insurers to return excess profits to policyholders who comply with risk management guidelines. It also provides for the formation of professional and commercial self-insurance funds and permits banks to own and control reinsurance companies.

Among the "tort reforms" in the act are provisions to replace joint and several liability with proportional liability, limit noneconomic damages to $450,000, and limit punitive damages to three times economic damages unless there is clear evidence that is not sufficient. Only 40 percent of punitive damages will go to the plaintiff, with the remainder going to the state.

Frederick B. Karl, lead attorney for the insurers, said he is pleased that the "tort reform" provisions were upheld and that a portion of the premium rebate section was struck down. "That is one of the sections that was most offensive to insurers," he said.

Insurance Commissioner Bill Gunter called the ruling "a tremendous victory for Florida business and professional insurance consumers." "The Florida law was more comprehensive than that of any other state, and yet it stood the test of an all-out legal challenge," he said. (*American Insurance Association et al. v. State of Florida, Dept. of Insurance, and Bill Gunter, Insurance Commissioner,* CirCt Leon Cty, No. 86-2262) □

D&O Coverage

SMALL COMPANIES DROP COVERAGE AS PREMIUMS RISE

Small- and mid-size companies faced with steep increases in liability insurance premiums are dropping directors' and officers' coverage, according to results of a nationwide survey of 41,000 companies released Oct. 28.

The cost of D&O insurance for small- and mid-size firms rose an average of 242 percent in 1986, according to Growth Resources Inc., a Massachusetts consulting firm that conducted the survey.

One third of the 41,000 firms surveyed reported that they did not renew their coverage. The remaining two-thirds said the coverage they purchased increased on average more than 400 percent. (The overall average increase therefore fell to 242 percent because no premium increase was reported for the one-third of firms that dropped their coverage.)

The average liability insurance premium per director in 1986 neared $2,700, up from $1,100 in 1985, Growth Resources reported. The average amount of liability coverage purchased was $3.5 million.

While 41 percent of the smaller companies' boards provided D&O coverage in 1985, only 31 percent provided it in 1986, according to the survey. "The removal of liability insurance coverage could put a crimp on the progress that has been made by so many small companies in attracting outside directors," said Richard Bronstein, president of Growth Resources.

"Some companies are getting around the problem of attracting qualified outsiders who may balk at serving as directors without liability insurance coverage by establishing advisory boards," Bronstein said. "While an advisory board cannot substitute for a board of directors, it can perform many valuable advisory functions and receive compensation without carrying the legal responsibilities of a board of directors," he said.

Growth Resources Inc. surveyed manufacturing, technology, and service companies with sales ranging from $250,000 to $60 million for the report. These firms' boards of directors had an average of five members each.

Copies of the *Seventh Edition 1986/87 Officer Compensation Report* are available for $425 from Growth Resources Inc., One Newbury St., Peabody, Mass. 01960. □

Damage Awards

$1 MILLION VERDICTS REDUCED BY HALF, ATLA REPORTS

Plaintiffs who won jury verdicts of $1 million or more in 1984 and 1985 actually received less than half the total amount of the money awarded, the Association of Trial Lawyers of America (ATLA) said in a report released Oct. 27.

While 198 verdicts examined totalled $790.6 million, the amount actually paid to plaintiffs was $339.2 million, an aggregate reduction of 57 percent, the report said.

The larger the original verdict, the larger the percentage reduction. While $1 million verdicts were reduced by 21 percent on average, $10 million verdicts were reduced by nearly 57 percent, it said.

The verdicts were examined by Dr. Ivy Broder, of the American University. Her findings were based on 198 cases out of a sample of 472 verdicts for $1 million or more provided by Jury Verdict Research Inc. She said the remaining 274 cases were still on appeal or were unusable because of confidentiality or other constraints.

The most severely injured received the highest verdicts and the highest settlements, Broder concluded. Her survey found that:

- The 22 paralysis victims received average verdicts of $4.1 million and settlements of $2.7 million;
- The 37 brain-damaged plaintiffs averaged $3.7 million in verdicts and $2.3 million in settlements; and
- The nine amputation cases had average verdicts of $3.5 million and average settlements of $2 million.

The less severely injured received the lowest average original verdicts and settlements, as well as the larger percentage reductions.

The wide variation in original verdicts is reduced through settlements, Broder said, suggesting that the settlement process provides a more consistent pattern of final awards. "Focusing on verdicts is quite misleading. A full picture of the way our judicial system actually compensates victims must include the actual settlement process as well as the results of jury deliberations."

The report, *An Analysis of Million Dollar Verdicts*, is available from ATLA, 1050 31st St. NW, Washington, DC 20007. □

Product Liability

PRESIDENT REAGAN URGED TO SIGN HEALTH LEGISLATION

Backers of the Omnibus Health Package passed in the final days of the 99th Congress are urging President Reagan to resist Justice Department officials' recommendations to veto the entire bill because of its provisions to create a vaccine injury compensation fund.

At a press conference Oct. 28 and in ads in the *New York Times* and the *Washington Times* Oct. 27, the supporters disputed the officials' arguments that the need for a no-fault compensation program for victims of vaccine-related injuries has not been proven.

The bill (S 1744), unanimously approved by the Senate Oct. 18 (*LIB*, Oct. 27, p. 3), is a comprehensive measure designed to promote exports of prescription drugs and compensate children injured by vaccines. It would also strengthen medical peer review and establish a national network to provide information on individual physicians' records.

"The potential for lawsuits has caused the price of the DPT vaccine to rise from $4.00 to $11.40 per dose in the last year alone," said Sen. Orrin G. Hatch (R-Utah), a cosponsor of the bill. "Insurers are reluctant to underwrite the liability, and, when they do the rates are high."

Hatch said the bill would make tort changes to reduce the unpredictability of damage awards against manufacturers and protect them if they meet government standards and requirements. "Most importantly, it will foster the development of safer vaccines," he said.

Even if signed by Reagan, the vaccine compensation program would not take effect until Congress approves a funding mechanism. □

Environmental Liability Coverage

EPA TO STUDY ASBESTOS HAZARD INSURANCE

Legislation requiring identification and abatement of asbestos hazards in some 31,000 public schools, signed by President Reagan Oct. 22, calls on the Environmental Protection Agency to study the availability of liability insurance for school boards and contractors doing the abatement work.

The Asbestos Hazard Emergency Response Act of 1986 provides for the establishment of federal requirements for inspection for asbestos-containing material and implementation of "appropriate response actions."

Sec. 210 of the law (PL 99-519) requires EPA to make a preliminary report on the availability of liability insurance for school agencies and contractors by April 1, 1988, and a final report by Oct. 1, 1990. It also authorizes the formation of insurance pools to cover injuries arising from the release of asbestos into the atmosphere during the abatement process.

The asbestos legislation specifically permits states to establish or modify liability standards for contractors or local education associations. □

Automobile Coverage

TWO INSURERS SEEK TO WITHDRAW FROM NEW JERSEY JUA

TRENTON, NJ — Firemen's Fund and Keystone Insurance Co. are seeking to withdraw as insurance carriers under the New Jersey Joint Underwriters Association (JUA) program, a state insurance department spokesman said Oct. 29.

A decision on the request will be announced "shortly," said spokesman Thomas Hooper, adding, "We have to approve it." The department has not yet received a formal application from Keystone, he said.

Citing a prospective $500 million deficit by 1988 in the JUA, Firemen's fund criticized the legislature for failing to enact proposed reforms. Hooper said the insurers "have no obligation to fund any deficit. That's what they're afraid of, but there is no danger of that."

The JUA, which covers nearly half of New Jersey's 3.8 million insured autos, contracts with individual insurers to cover those who are rejected in the voluntary market. Its rates are set at the same level as the voluntary market, Hooper said. "That's one of the problems."

Under state law, the companies must remain as part of the administrative structure of the JUA but are not required to serve as carriers, Hooper said. He said he does not think the withdrawal "will have any effect." The JUA has 15 carriers for 1.8 million cars, and loss of the two companies would affect only about 60,000 cars, he said.

Recommendations to increase the JUA's revenues, issued Sept. 16 by the Senate Special Committee on Automobile Insurance Reform, include: more efficient collection of surcharges on fines for accidents and violations; a second-tier rate for drivers with excess points for accidents and violations; stiffer fines for failure to maintain insurance; and a relaxation of the non-renewal law to "assist in depopulating" the JUA. □

New Jersey Tort, Insurance 'Reform'

PACKAGE OF 12 BILLS INTRODUCED IN LEGISLATURE

TRENTON, NJ — A 12-bill package of tort and insurance "reforms" was introduced in the New Jersey legislature Oct. 6.

The bills would give judges power to reduce jury verdicts, cap awards, and limit joint and several liability, as well as imposing financial disclosure, notification, and other requirements on insurers.

The package of bills is pending in the Senate Judiciary Committee and the Assembly Insurance Committee, a spokesman for Sen. Raymond Lesniak (D) told *LIB* Oct. 29. "We don't know when there will be action."

Lesniak's "tort reform" bill (S 2644) would allow judges to reduce or increase civil damage awards for personal injury if they find the awards "unreasonable" or the result of "mistake, prejudice or passion." A $500,000 cap would apply to all noneconomic damage awards except those involving "catastrophic" injury such as permanent, severe disability or disfigurement. The cap would not apply to medical costs.

The legislative package would amend joint and several liability provisions, which now permit a plaintiff to collect the total amount of an award from any defendant found 30 percent or more at fault if other defendants are unable to pay. The changes would eliminate joint and several liability for government agencies except in environmental torts. It would provide that defendants found 20 percent to 60 percent liable would pay only their share of noneconomic damages, while a defendant found more than 60 percent liable could be held responsible for all damages.

Other provisions in the bills would:

- Provide for structured payment of damage awards exceeding $200,000;
- Deduct collateral payments from damage awards;
- Permit stockholders to limit or eliminate liability for corporate directors and officers;
- Require arbitration of non-auto damage claims of $20,000 or less;
- Impose penalties of up to $2,500 for filing frivolous suits; and
- Limit dram shop and social host liability.

Among the insurance provisions in the legislative package are measures that would require financial disclosure by insurance companies, require a company to submit a plan if it intends to withdraw from a certain line of coverage "so the market won't be disrupted," and provide capital and surplus requirements for captive insurers, said Dale Davis, an Assembly Insurance Committee aide.

Lesniak's spokesman said the insurance provisions would also cover rate reductions and risk retention.

Davis told *LIB* the legislature is considering the "tort reform" measures first and probably will not take up the "insurance reform" bills until November or December.

The only insurance bill released for consideration by the legislature so far is S2318/A2404 on reporting requirements. Davis said the 12 bills, originally interlocked so that all or none would have to be enacted, have been "unhooked" for separate consideration. □

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Reinsurance

100 FIRMS FORCED OUT OF MARKET

NEW YORK — Some 100 competing reinsurers have pulled out of the U.S. casualty business in the last two years, "mostly because they are bankrupt or will be," attorney Donald J. Greene told the Insurance Information Institute (III) Oct. 29.

Greene, senior partner of the New York firm of LeBoeuf, Lamb, Leiby & McRae, told the III's 11th annual research seminar that those firms were "losing their shirts" because of the "crisis" in the reinsurance business. "This was not a xenophobic decision or an intellectual exercise," he said.

"In the last two years, they used up all the premium, all the investment income on the surplus, all investment income on premium they were holding in reserve and all their loss reserves, so they had to pay out from their basic capital," he said.

Greene, who is U.S. counsel for Lloyd's of London, said Lloyd's has picked up some of the business left by bankrupt firms, but, when 100 markets disappear, "there is bound to be an economic dislocation."

Changes in the U.S. tort system could improve the situation, he said. "Right now [the system's] lack of predictability is such that insurers and reinsurers would rather devote their capital and risk taking know-how to other lines of insurance in other parts of the world," he said.

Greene said the industry should fight any attempt by the federal government to regulate the reinsurance business, saying it is already adequately monitored by the states. "It's inevitable that the federal government will inquire into reinsurance," he said, but the additional red tape created would only aggravate problems by raising costs.

Enactment of the new legislation amending the Risk Retention Act (See related story, this issue.) "will have a big impact on the business," Greene predicted. "People who can't afford commercial insurance will consider this alternative." □

Product Liability

INSURANCE COSTS DETER AIDS VACCINE

High liability insurance costs are partly responsible for delaying the development of a vaccine against AIDS, the cochairman of a National Academy of Sciences panel on the disease said Oct. 29.

"Even if the scientific obstacles were surmounted, legal, social, and ethical factors could delay or limit the availability of an AIDS vaccine," Dr. David Baltimore, director of the Whitehead Institute for Biomedical Research and professor of biology at the Massachusetts Institute of Technology, said at a press conference at NAS.

Roy Widdus, project director for the NAS report *Confronting AIDS — Directions for Public Health, Health Care, and Research*, said several recent academy studies have found that court awards to persons claiming injuries from vaccines have a chilling effect on the development of new vaccines. "This general climate of uncertainty is something that deters many pharmaceutical companies from being involved in AIDS vaccine research," he said.

Many pharmaceutical firms self-insure for liability up to certain limits but have trouble finding companies that will provide coverage beyond those limits, Widdus said. "So, if they can't insure, they don't develop the vaccine."

Firms also hesitate to develop AIDS vaccines because the market is not large enough to justify potential liability losses, Widdus said. □

Medical Malpractice

18 PERCENT HIKE PASSED IN GEORGIA

ATLANTA — Georgia Insurance Commissioner Warren D. Evans has accepted a consent order permitting an 18 percent hike in physician's malpractice insurance by the St. Paul Companies in return for the elimination of the insurer's 8.5 percent surcharge plan.

Evans announced his decision Oct. 27, following a public hearing on Oct. 15 (*LIB*, Oct. 20, p. 3).

"After I ordered the hearing, the St. Paul Companies provided the Insurance Department with considerably more documentation than they did in their original rate filing," Evans said. "This additional data, plus St. Paul's offer to drop their 8.5 percent surcharge, were the deciding factors."

Evans had favored the surcharge plan because in theory it would mean higher premiums for doctors who have had malpractice claims filed against them. He said he changed his mind following protests from the medical community.

St. Paul instituted the surcharge plan following the department's denial of an average 62.3 increase in medical malpractice rates. An across-the-board 38 percent increase was later granted, but St. Paul said that rate hike was not enough. The company insures some 5,200 of the state's 9,000 doctors.

St. Paul subsequently said it planned to proceed with an additional 18 percent rate hike as well as the surcharge plan. Although Evans approved the surcharge, he denied the 18 percent increase. When St. Paul forged ahead with the increase anyway, Evans called for the public hearing to clear up the dispute.

"I hope the challenging of this rate filing will make it clear to all companies that any proposed rate increases must be supported by a well-documented need for such an increase," Evans said. □

Directors' Liability

TAKEOVERS SAID TO INCREASE SUITS

LOS ANGELES — Directors who worry about their exposure to liability from shareholder suits can help themselves by remembering that they represent the interests of shareholders, not management, an attorney told the National Association of Corporate Directors Oct. 21.

Lowell E. Sachnoff, of Chicago's Sachnoff, Weaver & Rubinstein, said the wave of corporate takeovers has generated the growth in suits against directors. "The courts have recognized that takeover situations necessarily involve the possibility of conflict of interest and implicate possible entrenchment motives and so are applying different rules to defensive actions."

The business judgment rule, which once extended almost complete protection to the business decisions of directors, no longer automatically applies in takeover situations. To find shelter under the rule, Sachnoff said, directors now have an "enhanced duty" to show good faith and lack of entrenchment motive during a hostile bid. The initial burden of proof in showing the reasonableness of defensive tactics, in relation to the threat posed, also lies with directors, he said.

The view that corporations should never be subject to a hostile tender offer and should resist at all times has been rejected by the courts, Sachnoff said, adding that courts condone certain defensive tactics.

Directors who want to keep themselves and their pocketbooks intact during hostile bids for the company should be prepared with an in-house defense team in advance of any such bid, Sachnoff said. The directors' and officers' insurance policy should be reviewed for complete coverage, he said. Outside experts (such as counsel, investment bankers, and proxy solicitors) should be retained only as needed, he said. □

Governmental Immunity

FIRE FIGHTERS SHIELDED, COURT RULES

Volunteer fire companies are entitled to governmental immunity from suits over damage caused by chemical agents used to extinguish fires, the Commonwealth Court of Pennsylvania ruled Oct. 16.

The appeals court upheld a trial court's ruling that volunteer fire companies are "local agencies" as defined under Pennsylvania law, holding that volunteer fire companies act on behalf of local government units.

In this case, the Dravosburg Volunteer Fire Dept. No. 1 and the Dravosburg Volunteer Co. No. 2 were summoned in April 1983 to clean up a diesel fuel spill on a highway adjacent to the lakes on which Beverly Wilson maintained a fishing operation. The fire companies applied a liquid chemical to the highway to disperse the fuel. Wilson filed a complaint of trespass in Allegheny County Common Pleas Court, alleging that this procedure polluted nearby lakes, thus causing the destruction of various fish and other aquatic life.

The trial court sustained preliminary objections filed by the fire companies arguing that the complaint should be dismissed as it involved them because they are entitled to immunity under Pennsylvania's 1980 Immunity Act.

In performing public fire fighting duties, volunteer fire companies act on behalf of local government units, the court held. This conclusion is supported by the historical and structural relationship between volunteer fire companies and the local municipalities and citizenry they serve, it said, affirming the order of the Allegheny County Common Pleas Court. *(Wilson v. Dravosburg Volunteer Fire Dept. No. 1*, Pa CmmwlthCt, No. 2813 CD 1984). □

Self Insurance

REINSURER SOUGHT FOR NEW OIL CAPTIVE

LONDON — Lead underwriters will soon be approached to provide reinsurance for a new oil industry captive, a spokesman for the broker arranging the transaction told *LIB* Oct. 15.

The captive, Oil Casualty Insurance Ltd. (OCIL), was launched from Bermuda in June by 24 leading energy groups. Reinsurance for the captive will be arranged by broker Alexander & Alexander, a source in the London subsidiary Alexander Howden Group said.

The founders of OCIL are all members of the 35-member Oil Insurance Ltd. (OIL), one of the biggest mutual underwriters in the industry. Despite the parallel membership of the two companies, OCIL is not a subsidiary of OIL, and the two will run separately.

"OIL was formed to provide seepage and other pollution cover, while OCIL has been formed due to great difficulty obtaining umbrella liability coverage," the source at Alexander Howden said. Some companies that were able to get coverage found it inadequate and will use OCIL for "topping up," he said.

Most of the companies that have joined OCIL are North American firms, including Standard Oil of Ohio, Sun Co., and Phillips. Some of them might have "gone bare" before the formation of OCIL, he said.

OCIL will write $100 million excess above $20 million on general, or umbrella, liability risks. It will cover up to $50 million excess above $20 million on directors' and officers' business but has an absolute exclusion on seepage and pollution. □

Medical Malpractice

RISK MANAGERS TOLD TO STRENGTHEN REVIEW OF DOCTORS

Congress is more likely to pass legislation aimed at disciplining incompetent doctors than at changing the tort system, Edmund Rice, director of federal relations for the American Hospital Association (AHA), said Oct. 25.

Rice told the AHA's annual meeting for hospital risk managers that broad-based "tort reform" at the federal level is "highly unlikely," but he predicted some 20 states would pass such "reforms" in 1987.

The Omnibus Health Package (S 1744), passed on the final day of the 99th Congress reflects legislators' desire to deal with the medical malpractice "crisis" by strengthening peer review processes rather than shielding physicians and hospitals from liability, Rice said. (See related story, this issue.) He said AHA supports the bill because the alternative is more "onerous."

The legislation, not yet signed by President Reagan, would provide legal immunity for physicians participating in peer review and would create a national information network to monitor physicians' records. It would require hospitals to report whenever a physician is disciplined.

Others also urged the risk managers to strengthen credentialing and review procedures for doctors as a protection against liability for hospitals in medical malpractice cases.

"The plaintiffs' bar is hauling hospitals into lawsuits on the theory of negligent credentialing," said Patti G. Zimmerman, an attorney with Baltimore's Smith, Somerville & Case. "Thus 'reasonable' or 'ordinary care' is going to mean hospitals must investigate all of the information they receive on a physician's application."

Zimmerman, who has defended hospitals in malpractice suits, said each hospital must adopt a credentialing policy and follow it religiously when reviewing applications. "Set a policy that requires a detailed investigation of the information provided and then follow it to the letter," she said. "The policy must be applied in exactly the same way to physicians who are seeking a renewal of the privileges," she said.

Hospitals must establish an annual evaluation for practicing physicians as well, Zimmerman said.

State statutes will not protect an application or a risk manager's investigation of the application from discovery proceedings, so the file should be prepared "as if a plaintiff's lawyer is going to see it," Zimmerman said. Hospitals should include as many issues as possible under the definition of medical review, she said, because medical review and quality assurance records are protected by state laws.

The Risk Retention Amendments of 1986, signed by Reagan Oct. 27, should be seen as a "step forward" because hospitals that participate in risk retention groups will be able to negotiate better rates with insurers, Rice told the group. "Hospitals can't be jacked back and forth with this legislation," he said.

Rice urged hospital risk managers to plan participation in risk retention groups soon, saying he expects the legislation to go into effect by mid-summer. □

Self Insurance

CONNECTICUT HOSPITALS BYPASS MARKET

HARTFORD, Conn. — Ten small, non-profit Connecticut hospitals have formed their own insurance company, Connmed, to bypass the commercial market for general and professional liability claims.

"We seemed to be at the mercy of the marketplace, and we all felt we ought to gain some control over our destiny," said Alfred Lerz, president of Johnson Memorial Hospital in Stafford Springs, Conn.

Connmed began operation Oct. 1, and Lerz said he is pleased so far with the results. The annual premium for his 78-bed hospital dropped from $500,000 last year to $330,000, he said. Some of that apparent savings won't be realized, he said, because the new system shifts from an "occurrence" to a "claims made" basis.

"In the first couple of years, we'll probably keep the premiums up to build up a kitty," said Robert Boardman, director of Rockville General.

The hospitals will benefit by being able to control their investment money until claims are actually made, said Albert May, spokesman for the Connecticut Hospital Association. The association is managing the new company, which offers its members coverage of up to $3 million. A commercial firm, Trenwick America Reinsurance Corp., of Westport, Conn., handles umbrella coverage over that amount.

Lerz, whose premiums rose 400 percent last year, said reinsurance has not been as big a problem for hospitals as primary coverage. The other hospitals now involved with the new company are: Bradley Memorial, Rockville General, Windham Community Memorial, Winsted Memorial, Griffin, Milford, New Milford, Sharon, and Park City.

Hospital officials said Connmed is the first such company in New England for small institutions, although some of the major non-profit hospitals have been taking steps toward at least partial self-insurance to avoid the commercial market. Lerz said some small hospitals in New Hampshire have expressed interest in joining Connmed when it accepts new members next fall. □

VERDICTS & SETTLEMENTS

■ Manville Corp. has reached a $62.1 million settlement with a group of syndicates at Lloyd's of London and other firms participating with its underwriters. Manville sued Lloyd's and 26 other carriers seeking a determination of their obligations to pay for losses arising out of asbestos-related and other claims. The settlement will be paid in three installments. *(Johns-Manville v. Home Insurance, et al., Calif SuperCt (San Francisco), No. 765226, 10/24/86)*

■ A Los Angeles Superior Court judge has upheld a $23.7 million award to Nichole Fortman, a 9-year-old whose fall out of a jeep in 1981 left her paralyzed and brain-damaged. Hemco Inc., which produced the mold for the vehicle's fiberglass doors, must pay Nichole $6 million for pain and suffering and $17.7 million for medical expenses and lost earnings. No punitive damages were awarded. Hemco's mold was allegedly defective because the doors were rear-hinged. A separate settlement was reached with Jeep Corp. *(Fortman v. Hemco Inc., LA SuperCt, NWC 86375, 10/15/86)*

■ A New York Supreme Court jury has found tennis star Martina Navratilova not liable for damages suffered by photographer Arthur Seitz during a scuffle following her loss in a 1982 tournament, although it awarded Seitz $50 for exposed film. Seitz sued Navratilova for $2 million, charging that she struck him and caused him to develop a calcium deposit on his arm that required surgery. Navratilova countersued for $4.5 million, alleging that the incident caused her "psychological damage." The jury foreman said the panel did not condone Navratilova's conduct but found Seitz too "pushy." *(Seitz v. Navratilova, NY SupCt, Suffolk Cty, No. 024672/84, 10/9/86)*

■ The Montana Supreme Court has ordered George Ellinghouse to either accept $1 million in place of a jury's $5.2 million award against an insurer or submit to a new trial. Ellinghouse, who provided consulting services for a golf-course sprinkler system in 1974, was sued when a man was electrocuted while digging near the system's underground wires. Safeco initially accepted coverage and defense of the case but pulled out two months before the trial. While the evidence is sufficient to sustain a verdict against Safeco, the court ruled, it does not show a vindictiveness or ill will so extreme as to warrant the "exorbitant sum " awarded by the jury. *(Safeco Insurance Co. v. Ellinghouse, Montana SupCt, No. 85-257, 9/17/86)*

Municipal Coverage

WEST VIRGINIA PLAN ENROLLS 115

CHARLESTON, WVa. — More than 115 local governments have joined West Virginia's new state-run insurance program for liability coverage, according to Robert Corey, director of the state's Board of Risk & Insurance Management.

The government units and nonprofit organizations will pay $6 million in annual premiums, Corey said, adding that he is now confident the state can successfully run the insurance program.

Jim Mahurin, a consultant who negotiated the policy for the Raleigh County Commission, said officials there expect to save $39,144 in premiums the first year and receive greater coverage as well. "But the state needs to exercise extreme caution because it could be an extreme money-loser," he said.

West Virginia has operated a pool since 1971 for its state agencies, and county school boards were allowed to join in 1980, Corey said. The plan, which covers 89,000 employees, could cover an additional 25,000, he said.

The state's new program will cover all claims, Corey said. If total claims prove higher than premiums, the state can always raise its rates or impose deductibles, he said.

The program was required by an executive order issued this year by Gov. Arch A. Moore Jr. (R). □

LIABILITY & INSURANCE BULLETIN

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Tab 79

MEDICINE...
DESIGNED FOR HEALTH...
PRODUCED WITH CARE

THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001
TELEPHONE (616) 382-4000

PHARMACEUTICAL RESEARCH
AND DEVELOPMENT

FDA LIAISON
Office of
D. J. MASON, PH.D.
Manager

September 10, 1970

Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20852

#5

Reference: IND for Compressed Tablets U-33,030 (Original Submission)

Gentlemen:

We are submitting, under the provisions of section 505(i) of the Federal Food, Drug and Cosmetic Act and section 130.3 of Title 21 of the Code of Federal Regulations, three copies of a Claim for Investigational Exemption for Compressed Tablets U-33,030.

This filing is intended to cover Phase 1 studies of U-33,030 as an anti-anxiety agent.

Sincerely yours,

THE UPJOHN COMPANY

D. J. Mason, Ph.D.

DJM/mak

9005592

Tab 80

THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001
TELEPHONE (616) 382-4000

DRUG REGULATORY AFFAIRS
Pharmaceutical Research and Development
Office of
E. L. SCHUMANN, PH.D.
Director

May 4, 1976

Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Reference: New Drug Application for Compressed Tablets Halcion® (triazolam)
(Original Submission)

Gentlemen:

We are submitting under the provisions of section 314.1 of Title 21, Code of Federal Regulations, a New Drug Application for Compressed Tablets Halcion (triazolam). This drug is a benzodiazepine type compound intended for the treatment of insomnia.

There are 147 volumes in this application; they are submitted as follows:

Three copies of the following:

Volume 1.1 - Part 1, Contents
Part 2, Optional Expanded Summary

Volumes 1.2 through 1.17 - Expanded Summary (continued from Volume 1.1)

Volume 1.18 - Summary of Dependence Liability Studies
(Note: In addition to the three review copies, 15 additional copies of Volume 1.18 are included for your Drug Abuse Staff.)

Volume 1.19 - Part 4, Labeling
Part 5, Statement
Part 6, List of Articles
Part 7, Composition of Drug
Part 8, Methods and Controls
Part 9, Drug Samples; Description of Reference Standard

Volumes 1.20 through 1.23 - Part 10, Pre[illegible]inical Studies

Volume 1.24 - Part 11, List of Investigators
Part 12, Clinical Studies
Part 13, Statement
Part 14, Environmental Impact Analysis Report

Two copies of the following:

Volumes 1.25 (RR1) through 1.28 (RR4) - Drug Experience Reports (FD-1639's)

One copy of the following:

Volumes 1.29 (C1) through 1.129 (C101) - Patient Case Record

Volumes 1.130 (PS1) through 1.147 (PS18) - Computer Generated Patient Summaries

Under separate cover, the following samples are submitted with this application:

New Drug Substance (Bulk Drug):

Lot 8257-CH-141, 1 bottle, 1 gram
Lot 11324-TGS-33, 1 bottle, 1 gram
Lot 11324-TGS-87, 1 bottle, 1 gram

Finished Product:

C. T. triazolam 0.25 mg -

Lot 17,543-2	4 bottles	150 each
Lot 17,543-5	4 bottles	150 each
Lot INV 2494	4 bottles	150 each

C. T. triazolam 0.5 mg -

Lot 17,544-2	4 bottles	150 each
Lot 17,544-5	4 bottles	150 each
Lot INV 2495	4 bottles	150 each

C. T. triazolam 1 mg -

Lot 17,545-1	4 bottles	150 each
Lot 17,545-2	4 bottles	150 each
Lot INV 2496	4 bottles	150 each

Control Reference Standard Issue A

Lot 8257-CH-86	10 vials	250 mg each

May 4, 1976

The studies described in this NDA were conducted under IND-7231, C. T. U-33,030; that IND may be referred to in the review of this submission.

Sincerely yours,

THE UPJOHN COMPANY

E. L. Schumann

E. L. Schumann, Ph.D.

ELS/ekj
Attachments

Tab 81

Food and Drug Administration
Rockville MD 20857

COPY

NDA 17-892

NOV 15 1982

The Upjohn Company
Attention: E.L. Schumann, Ph.D.
Kalamazoo, Michigan 49001

Gentlemen:

Please refer to your new drug application dated May 4, 1976 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Compressed Tablets Halcion (triazolam), 0.25 mg and 0.5 mg, NDA 17-892.

We also refer to our letters dated February 26, 1982 and October 25, 1982, and to your additional communication of October 28, 1982.

We have completed the review of this application as amended and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

As detailed in our February 26, 1982 letter, and reaffirmed in our letter of October 25, 1982, it is required that you perform a Phase IV dose proportionality study in healthy volunteers as a condition of approval.

Also, it is understood that approval of this NDA is conditional upon the announcement of the final scheduling decision in the Federal Register by the Drug Enforcement Administration.

The enclosures summarize the remaining conditions relating to the approval of this application.

Please submit one market package of the drug when available.

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Acting Director
Office of New Drug Evaluation
National Center for Drugs and Biologics

Enclosures: Records and Reports Requirement (Reg. 310.300)
Conditions of Approval of an NDA

0416406

Tab 82

venting Reagan from being Reagan. The Administration was caving in on a tax hike. Violations of SALT II were being ignored. Policy regarding Poland was an enigma. Drift.

Well, Baker, Deaver, and Darman are gone. Donald Regan and even Pat Buchanan are in place. And here we are, dismantling a Poseidon to conform with SALT II. Not a thing was done about the murder of Major Nicholson. Not a thing has been done about the murder of Robert Stethem by the hijackers. It's business as usual in the terrorist camps of the Bekaa Valley. (François Mitterrand was tougher: The French bombed the Bekaa and their nationals have since been let alone.) The Administration was strangely passive during the appropriations fight over Star Wars, funding was reduced, and rumors circulate that George Shultz and Robert McFarlane are going to sell out on Star Wars in exchange for a cosmetic reduction in Soviet warheads. The forthcoming summit meeting with Gorbachev appears to be politically stacked in his favor. He at least has an agenda: ending Star Wars. Our agenda appears to consist only of a vague desire for "peace."

The Pentagon issues ridiculous pronunciamentos explaining why it cannot use force here, there—anywhere? It seems to have a George McClellan complex.

Which brings us to Secretary of State George Shultz. Now, George Shultz has never been in danger of being mistaken for Julius Caesar. But Shultz has now given a tough speech at Helsinki, and he was one of the hard-liners within the Administration on the recent hostage affair. Shultz wants to hit back. So does Secretary of Education William Bennett. Reflect on that. The Secretary of Education took a tougher position than the Pentagon. Shultz is entirely absorbed by the State Department apparatus, but he is not the source of the trouble.

Someone is supposed to be in charge down there.

Liability Nightmare

"ITEM: A man sticks his two-year-old son's head between the running blades of a ceiling fan—and then sues the manufacturer for failing to warn him the child might be injured.

"Item: A company that had manufactured textile machinery for 136 years goes out of business because of the costs of liability lawsuits over equipment it had manufactured decades earlier.

"Item: After deciding that a drug a woman had taken during pregnancy was not responsible for her child's birth defects, a jury awarded her damages anyway—to help defray medical costs of the child's future care."

These horror stories, culled by a Heritage Foundation researcher, show why product-liability law has become a menace to more than just the Manvilles and Union Carbides of the world. Even without a single obvious disaster, the case-by-case costs of litigation can drive small companies to the wall. Heritage analyst Milton Copulos says 20 per cent of the cost of an ordinary stepladder is traceable to past, present, and future liability.

Sad to say, the horror stories are not mere flukes; each one illustrates a principle of law. The ceiling-fan case is just one example of how courts are disallowing the traditional defense of contributory negligence. Another such case involved a man who strapped a refrigerator to his back and ran a stunt footrace. One of the straps failed, and he collected $1 million from the strap manufacturer.

The textile-machinery case shows how a company can be assessed damages for injuries caused by long-forgotten, impossible-to-track-down products. The drug case typifies the new doctrine of generic liability, under which a consumer who suffers side-effects after taking a pill and cannot remember which brand he took can successfully sue *all* the makers of the compound in question.

The big winners—did you have any doubt?—are the lawyers. A Rand study found that a typical court case cost $380,000, of which $125,000 went to the defense lawyers, $114,000 to the plaintiff's lawyers, and $141,000 in net compensation to the plaintiff.

One of the ironies of the liability spiral is that in some areas it is making life more risky as well as more expensive. Sears was sued by a heart-attack victim who claimed that its lawnmower starter cord was too hard to pull; but rectifying this "defect" would make it easier for children to endanger themselves by activating the machines. Edmund Kitch, writing in a recent issue of *Regulation*, tells how liability for rare side-effects is driving many manufacturers out of the vaccine market, even in cases where united medical opinion agrees that the vaccines do more good than harm overall.

The diphtheria-tetanus-whooping-cough vaccine for children now costs $2.80 a dose and rising, up from ten cents a while back. Worse yet is the problem of "orphan vaccines." Although medical research continues to progress toward the hope of vaccines against AIDS and herpes, Kitch says that "testing and obtaining regulatory clearance for such vaccines is not currently of interest to any potential producer. Those invisible non-litigants who would benefit from new vaccines are probably the most dramatic victims of the threat of product-liability law."

Smeal Time

THE STRUGGLE for the presidency of the National Organization for Women pitted Eleanor Smeal, a former president, against the incumbent, Judy Goldsmith, a former Smeal protégée. It turned on degrees

Tab 83

REMARKS OF

DOUGLAS A. RIGGS

GENERAL COUNSEL OF THE U.S. DEPARTMENT OF COMMERCE

ON THE CAUSES OF THE INSURANCE

AND PRODUCT LIABILITY CRISIS

PRESENTED BEFORE:

MAIN HURDMAN, CPA
ANNUAL PARTNER'S MEETING
MIAMI, FLORIDA
JUNE 26, 1986

AMERICAN SOCIETY OF HEATING, REFRIGERATING,
AND AIR-CONDITIONING ENGINEERS, INC.
ANNUAL MEETING
PORTLAND, OREGON
JUNE 23, 1986

It is a pleasure to be here with you this morning to discuss a topic which many Americans, especially in the business community, consider the number one economic issue facing America today: namely, the need for tort reform, particularly of our product liability laws.

Some of you in this audience may not believe tort reform concerns you. If so, well, you are wrong. As certified public accountants, you are directly affected by professional liability costs. Moreover, many if not most of your clients are affected by numerous tort issues. Finally, each of you is a consumer, and consumers as a group ultimately pay the costs associated with tort losses.

For all these reasons, you should be concerned about -- and involved in -- the current public debate over tort reform.

I know that there is a tort crisis because in the last few months, I have responded to literally hundreds of letters and spoken to thousands in business and civic groups on this issue. All across the country, people are unable to obtain liability insurance at affordable rates and, in some cases, to obtain insurance at all. Unlike a few years ago, when this problem affected only a few small groups in our society -- like doctors -- today's crisis has no bounds.

Manufacturers and sellers of virtually every product or service, professionals, such as lawyers, engineers and -- yes -- accountants, and municipalities of every size are encountering serious problems arising from premium increases, policy cancellations and refusals to underwrite certain activities.

While a number of causes have been suggested for these problems, I believe the excesses that have crept into our legal system are the single most important factor contributing to the liability insurance crisis, particularly in the area of product liability.

The costs associated with tort awards, including the cost of liability insurance, are passed along to consumers in the form of higher prices, and in many cases result in the loss of socially beneficial products and of jobs. So, our legal excesses have clear and detrimental effects on our domestic economy and our international competitiveness.

But before I go further into that side of the problem, let me take a moment to explain how our insurance system affects and is affected by our legal system.

Though severe injuries and losses rarely occur, they can be devastating. For this reason, most people are willing to take on a minimal, but certain, financial obligation in return for protection against the unlikely, but potentially overwhelming, one. That is why insurance exists. You all know this. You all have bought insurance to protect against uncommon risks, be they from natural disaster, theft, or a civil wrong.

Product liability insurance exists for the same reason. Some companies will, despite quality control efforts, occasionally produce a defective product which severely hurts a user. In many cases, even such unintentional behavior will constitute the breach of a legal duty, something we lawyers call a "tort." The cost of compensating such tort victims can be many times company earnings, especially in the case of small businesses. Such a result would be devastating to any company whether it is large or small.

By spreading this cost among all producers, product liability coverage makes it possible for companies to manufacture and sell despite the risk of liability for a defective product and the costs associated with a lawsuit. This is why product liability insurance is called "a linchpin in the operation of our economy." Without it, the wheels of production would grind to a halt.

It is a system in which the onus to insure falls on the potential tortfeasors and defendants rather than on the potential victims and plaintiffs. Through our civil justice and insurance systems, the cost of product harm is transferred from users to producers. In this way, overall prices come to reflect the "social costs" associated with the manufacture, use and sale of products, and producers have a direct incentive to reduce the likelihood of product-caused accidents.

Traditionally, insurance companies invest premiums until they must be applied against claims. During the late 1970's, soaring interest rates made it feasible for insurance companies to undercharge for coverage in order to attract more cash for investment. A price war raged for several years, with insurance companies offering more and more coverage for less and less money. You probably have all heard of this practice -- it is commonly referred to as "cash flow underwriting."

While this may have been a reasonable response to the short-term incentives of the investment market, it disrupted the accident-reducing function of product liability insurance. Not only were potential injury claims spread among more producers, but the true costs of those injuries were masked by the interest rate subsidy. Unintentionally, perhaps, the insurance companies were sending the

wrong signal to manufacturers and to the American public. From the prices charged for premiums, it appeared that injury claims and the amounts awarded were declining when, in fact, they were going up significantly.

This increase in claims and awards was fueled in no small part by the fact that the common law of tort was undergoing radical change. Although the basis of tort law is fault, there is another important theory -- somewhat more recent -- called "strict liability." This theory holds that in certain cases, a party should be liable for the consequences of his acts regardless of fault.

Initially, this concept was subject to substantial legal limitations. Strict liability was seen as an exception to the rule, and therefore used sparingly. Beginning in the 1960's, however, legal scholars and judges expanded upon the notion of strict liability and developed new theories of recovery, creating new legal duties and additional categories of damages. Strict liability began to be applied without regard to its original limitations. In some jurisdictions, strict liability bordered on absolute liability.

In part, these new interpretations drew upon the new dangers of advanced technology and our growing ability to trace disease and injury to chemical and other sources. In part, they reflected confidence in our prosperity as a nation and the view that we could afford to compensate for every harm. And in part, I must admit, they stemmed from the pressure generated by record numbers of attorneys seeking to earn a living and exercise their creative talents.

But more important, and to no small extent, these efforts reflected a desire to achieve a particular ideological goal -- a risk-free society, or at the very least, a society in which no one would have to bear, without compensation, what Shakespeare called the "slings and arrows of outrageous fortune." This was to be part of the "great society:" every person entitled to be made whole, regardless of the circumstances of his injury.

This legal policy was nothing short of an off-budget mechanism for redistributing wealth in the United States. This policy reflected, if not promoted, the belief that whenever there are personal injuries, the people -- "us" -- are owed something by institutions -- "them" -- particularly by America's businesses and governmental bodies. Regardless of the degree of fault attributable to the injured or to third parties, those with the deepest pockets are "expected" to fork over compensation.

Furthermore our technological advances and new insights into causes and effects make us more aware of the risks in daily life. This awareness, coupled with subtle but real attitude changes in our society, have made us less willing to assume many of those risks. Where Alexander Woollcott could once quip, "all the things I really like are either illegal, immoral or fattening," today we might say, without much humor, "everything we enjoy is either infectious, carcinogenic or promotes hardening of the arteries" -- but we can sue!

This propensity to sue, coupled with the expansion of tort doctrine and the willingness of juries and judges to award spectacular damages, made the '70's (and '80's) a time for exploding tort liability. The inflation and interest rates which lowered the cost of insurance, raised the amount of tort damages and paved the way for the multi-million dollar verdicts which have become almost commonplace.

The proverbial chickens have flocked home to roost since 1983 when inflation and interest rates started their drop to the lowest levels in over a decade under the leadership of President Reagan. Of course, we can all be grateful for that. But a side effect has been a precipitous decline in insurance company revenues. Thus, as tort suits and judgments have skyrocketed, insurance companies have suffered staggering underwriting losses paying out record claims.

Insurance companies have responded to this squeeze by tremendously raising product liability premiums and reducing or eliminating many forms of coverage. We have received reports of up to 1000% increases! Though it is impossible to recoup past losses, those companies appear to have decided not to make the same mistake twice. This time they are pricing policies on the basis of the costs of the tort system, rather than on the interest rate index.

Whereas their earlier undercharges masked the true costs of coverage, today's insurance (including in some instances the lack thereof) reflects the reality of the costs associated with the tort system. As a result, the consumer and the manufacturer have had to come to grips with the true price of the risk-free society.

We must remember that insurance is a consensual, commercial arrangement which comes about as a result of needs. Coverage will be available only as long as those who need it are willing to pay premiums sufficient to pay for it -- that is, to cover their losses and allow a reasonable profit for those providing the insurance.

In some cases, however, realistically priced insurance will be so expensive that manufacturers will not be able to afford to produce. In theory, I suppose, that's not a bad thing: if your product turns out to be harmful to the public, you should stop making it. That's how fault-based liability increases consumer safety.

But that's not always the way it works. Tremendous judgments are being awarded even when products are not unreasonably dangerous, even when the manufacturer or seller is not at fault, but simply because he has a deep pocket. The result is that products which are not unsafe, which consumers want and need, are pulled from the shelves. And there are dozens of foreign-made products waiting to replace them.

A recent example of this phenomenon was the massive swine flu immunization program. After a series of lawsuits, the manufacturers announced that they could no longer afford to produce the vaccine. Although it was clear that, on balance, the risk of adverse reactions was small compared to the benefits, the few harmed by the vaccine collected awards large enough to endanger the entire program.

The government, including Congress, believed the vaccine was essential to public health, and used taxpayer dollars to underwrite the pharmaceutical companies so that production could continue. But we can't afford to do that every time: moreover, it goes against our grain to have Uncle Sam do so.

However, if our tort system continues in this direction, we will find ourselves in situations like this more and more. As coverage becomes increasingly unaffordable and even unavailable, manufacturers and businesses will shut down: and the first to go will be the small ones, the entrepreneurs who constitute the vital lifeblood of our economy.

It is utter nonsense to assert that the crisis will be cured by government regulation of the insurance industry rather than reform of tort law. Shall we require that industry to operate some of its lines of coverage at a loss in order to subsidize the tort system? I don't think so. Moreover, even to contemplate such a result is to turn our free enterprise system on its head; but someone has to pay the piper if we want to compensate all victims generously.

Many people remark that Britain, France and Japan have less litigious societies than America, and that manufacturers in those countries have far fewer problems with the availability and affordability of product liability insurance. The key difference is that the governments of those countries undertake as a public

function the underwriting of health care and other social costs for their citizens -- action that the United States has undertaken only in exceptional situations, such as the swine flu case.

Those countries' governments underwrite the risks of modern life by heavily taxing their people. Fortunately, we in America have rejected the socialist notion that the central government knows best and provides best, choosing instead the risks -- but potential gains -- of free enterprise.

Of course in all countries, including the United States, consumers as a group ultimately pay the costs associated with the suits of the injured few. But there are two distinguishing features between our policy and that of those other countries.

First, victims recover far less in those countries for their injuries. And second, -- and I believe it to be a very important distinction -- the incentive structures are different. With costs spread through the tax system in the other countries, there is no particular pressure applied to those in the best position to produce safer products. But if a manufacturer in the United States knows he will be sued if he produces harmful products, the profit incentive motivates him to make his products safer. He may spend a bit more on production, but he'll come out ahead in the long run. Only in America is there this kind of direct feedback to manufacturers and product sellers.

However, when the system goes berserk and rewards and punishes indiscriminately -- as I believe our system now does -- manufacturers have less incentive to be careful. If manufacturers know they are likely to land in court even if they're not at fault, the system breaks down. The erosion of the fault-based liability doctrine has blurred the distinction between a safe and an unsafe manufacturer and thereby destroyed the deterrence pillar of the tort law.

Our judicial system is largely responsible for this result. Activist judges have ignored the common law of tort, choosing instead to engage in a systematic re-interpretation of tort doctrine. They have steadily expanded legal duties in line with their own social/philosophical beliefs.

The American people should remind their judges that public policy should be debated and established in our <u>legislatures</u> -- <u>not in our court rooms</u>. Moreover, both judges and juries must come to understand that the tremendous sums they frequently award are not

paid out of some secret corporate fund. Rather, the money they hand out comes from all of us, as consumers, stockholders and taxpayers.

Until we curb the excesses in tort litigation, costs will continue to rise. This cannot go on. And it will not. A more rational, predictable tort system is required. It is time we realized that while there may be individual winners and losers in our present system, the total costs are borne by society as a whole.

Recently, a number of states have begun to take steps to address the excesses in their tort laws. Maryland has put a cap on non-economic damages. Florida has capped damages (at a different level) and has also modified its rule on joint and several liability. California voters recently approved Proposition 51 which re-establishes the traditional connection between a defendant's responsiblity for an injury and his obligation to pay non-economic damages. These are important steps and should be encouraged.

But each state addresses these problems in different ways. This reflects, among other things, the historical fact that the common law of tort has developed independently in each state. Because of this, the states are well suited to address most concerns in the tort law, such as those associated with medical malpractice, professional liability and municipal liability. These are issues where local views can and must be primary.

The product liability issue, however, poses a different problem. Because today's stream of commerce is apt to carry every product beyond the state in which it was made, questions of product liability inevitably raise interstate commerce concerns. Though the recent tort reform efforts undertaken by the individual states are certainly welcome and necessary, and reflect a recognition of the seriousness of the problem, we do not expect the states, each working independently, to produce a consistent product liability system. Interstate problems call for interstate solutions.

Among the responsibilities our Constitution explicitly delegates to the central government is the duty to regulate interstate commerce for the good of the whole. That is why we have proposed federal product liability legislation -- to provide a predictable set of standards upon which businesses and consumers alike can rely. The Federal government cannot abdicate its responsibility in this area and must take a leadership role -- which is precisely what this Administration intends to do.

In April, the President sent to Congress a bill which, as he described it, "would set an example of simple good sense for the rest of the Nation to follow." It will protect the free flow of goods in interstate commerce by placing reasonable limitations on the excesses of product liability law and returning it to a fault-based system. And it will not preempt all state action: the states would be free to adopt more stringent standards.

The bill would ensure that product liability law operates to compensate injuries caused by the wrongdoing of others. At the same time, it would reduce the unacceptably high transaction costs associated with litigation and would limit excessive awards.

In addition to requiring that liability be based on fault, the bill will limit the application of joint and several liability to situations where persons have acted in concert to cause an injury. The bill also reduces awards in cases where a plaintiff is eligible for certain collateral sources of compensation, such as Social Security Disability Benefits, workers' compensation or employer financed health care benefits.

In the area of damages, the bill will place a dollar cap on non-economic damages, including punitive damages. This cap will, of course, have no effect on the award of economic damages, such as medical care, rehabilitation costs or lost earnings. Awards of future economic damages which are greater than $100,000 will be paid periodically rather than in a single lump-sum. Courts will have the discretion to fix the level and schedule of payments at the time of judgment.

The bill also will help alleviate the enormous transaction costs associated with litigation by establishing a "sliding scale" for attorney contingency fees that decreases as the amount of an award increases.

The rising costs associated with product liability suits cause negative effects which ripple throughout our society. They have a detrimental effect on our country's productivity and competitiveness, and ultimately are reflected in the expenses of every consumer.

Already we have seen the effect of this run-away system: dozens of firms producing items ranging from health equipment to child car seats are discontinuing the manufacture of their products. This causes the loss of American jobs and hands our foreign competitors -- who are, by the way, far more difficult to sue -- yet another opportunity to profit at our expense.

Legislative action is needed -- and needed now -- to deal effectively with the situation.

The problems facing us today in our product liability system have developed over years and have many different roots. There is no quick fix. We must all work together, at the state and Federal level, using all three branches of government in close cooperation with business, consumer and labor interests to correct these problems.

Your contribution to this effort is needed and appreciated.

Thank you.

Tab 84

Evaluative Studies

This series of studies seeks to bring about greater understanding and promote continuing review of the activities and functions of the federal government. Each study focuses on a specific program, evaluating its costs and efficiency, the extent to which it achieves its objectives, and the major alternative means—public and private—for reaching those objectives. Yale Brozen, professor of economics at the University of Chicago and an adjunct scholar of the American Enterprise Institute for Public Policy Research, is the director of the program.

THE EXPECTED RETURN FROM PHARMACEUTICAL RESEARCH

Sources of new drugs and the profitability of R&D investment

David Schwartzman

American Enterprise Institute for Public Policy Research
Washington, D. C.

This study is one of a series published by the American Enterprise Institute as part of the research program of AEI's Center for Health Policy Research. A distinguished advisory committee, whose members are listed below, helps guide this program.

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CHAPTER I

INTRODUCTION

A rapid rise in the cost of medical services has placed the task of financing and controlling medical costs near the top of the nation's social policy agenda for the 1970s. Hospital insurance programs, Medicare, and Medicaid have increased the use and the prices of medical services, and enactment of a national health insurance scheme could be expected to worsen the problem. The total cost of medical care is approaching $100 billion and continues to rise.

The federal government supports and funds programs intended to produce better medical care at more reasonable prices—programs especially including health maintenance organizations (HMOs). Advocates of HMOs argue that greater use of such groups, which integrate health insurance with health care and reduce the fee for the service component of medical costs, will limit the pressure for overprescription of medical services. Overprescription tends to cause overuse and increased prices.

Besides possible overprescription, an important reason for the higher cost of medical care has been the development of new and costly medical technology. Kidney dialysis, open heart surgery, and coronary bypass implantation have added considerably to the burden of medical costs. Ethical drugs, on the other hand, help to relieve suffering at relatively small cost and, when they provide an alternative to expensive kinds of therapy, greatly decrease medical bills. This study focuses on the cost of drugs—not out of a desire to diminish their human benefits, but rather because the high costs of

* I would like to acknowledge the help of Merton J. Peck, John McGowan, John Owen, Solomon Fabricant, J. Fred Weston, and Yale Brozen who saw earlier drafts of the manuscript. The views expressed and any errors which might remain are of course my responsibility.

medical care are a matter of urgent concern and the costs of drugs are part of the costs of medical care.

The Role of Drugs

Since ethical drugs are a relatively inexpensive mode of therapy, it would seem clear that pharmaceutical industry R&D should be encouraged in order to increase the production of new ethical drugs. Paradoxically, the importance of the ethical drug industry in providing therapy has been neglected. Public attention has tended to be fixed, instead, on the profits and selling costs of the ethical drug manufacturers, even though profits and costs constitute a small fraction of the nation's total medical expenditures. Currently, U.S. sales of ethical drugs account for only $6 billion of total medical expenditures of over $90 billion, and total selling costs and profits account for very much less.

The opportunities for savings to be realized by a lowering of the prices of drugs are much less than the opportunities for savings to be realized in other components of the medical care industry. Any apparent savings from the cutting of drug prices would be more than counterbalanced if these savings had the effect of reducing the number of drug innovations, and so raising the total cost of medical care. In other words, when policy makers concentrate on correcting the presumed inequity of high prices of the drug industry, they are stressing a secondary problem, the remedies for which could well undercut attempts to solve the much more important problem of improving the quality and reducing the costs of medical care. Policies designed to decrease drug prices might produce some savings for consumers in the form of lower immediate expenditures for drugs but would risk the loss of much larger potential savings—both direct and indirect—that might flow from the development of new drugs. An emphasis on correcting high prices distorts any general economic analysis of the functions and performance of the industry: it places too much emphasis on the alleged monopoly problem, when other problems including that of encouraging innovation are more important.

Better understanding of drug industry performance is aided by viewing drug therapy as a relatively low-cost medical technology that may displace other more expensive technologies. For example, recent advances in drug research have promised drug therapies as a low-cost substitute for surgery for treating gallstones. Although the range of choice of technology may be limited for some diseases, this is not always the case: different technologies (surgery, radiology, intensive care, hospital care) may be used simultaneously or in sequence.

In fact, medical practitioners are not accustomed to a cost-benefit analysis of choices among alternative therapeutic methods. Their stated objective is to provide patients with the best available therapy regardless of cost. This approach has some moral advantages: a doctor need not restrict expensive but effective therapeutic programs to rich patients. But costs are relevant to medical decisions, and doctors should certainly choose an economical form of therapy when it is as safe as other forms.

When we compare medical technologies, it is immediately evident that drug therapy is more widely applicable than some other forms of treatment. More diseases can be treated by drugs than by surgery and radiology. The use of drugs thus permits larger reductions in morbidity and mortality rates than are permitted by alternative forms of treatment and, as a result, can bring larger reductions in the cost of disease.[1]

Alternative forms of therapy are much more costly than drugs because they rely on the employment of professional skills, costly equipment, or a large labor input per patient. Surgery, radiology, and intensive care require substantial outlays for both professional skills and equipment, and psychiatry, physical therapy, and hospital care demand large inputs of man-hours, whether professional or unskilled. The care of coronary disease, for example, employs teams of professional personnel and expensive equipment. The most dramatic current example of this is the heart transplant, and considerable research is currently directed to the development of an artificial heart. But expense prevents the use of heart transplants for a large number of patients. The development of costly (though successful) medical technology has contributed to the catastrophic costs of certain illnesses for individual families and thus (among other things) to current proposals for national health insurance.[2]

Not only is treatment by drug therapy intrinsically more desirable, but also it is more economical than alternative treatment. First, it is more economical because patients can usually take drugs without any assistance. In order to make self-administration easy, drugs should be made up in oral dosage forms rather than those that require injection; even though the development of an oral dosage form may not represent an important medical advance over a parenteral form, it may still be of economic importance. Second, it is more economical because most drugs are mass-produced rather than made up as required for each patient. The fact that drugs are mass-produced in appropriate dosage forms should not be taken for granted and is,

indeed, a relatively recent development. Before the 1940s, pharmacists did their own compounding for each prescription. The pharmaceutical manufacturers took over the manufacture of final dosage drugs in the 1940s and 1950s after the introduction of the sulfa drugs and the antibiotics. This development has greatly reduced the cost of operating a pharmacy and, to the extent that pharmaceutical retailing is competitive, has reduced the cost of prescriptions.

The introduction of mass production methods of drug manufacture represented a large increase in productivity. The new methods displaced what was virtually a handicraft technology—one that, with the increases in wages, had become quite expensive. The shift in production methods reflected the same economic forces as the shift to self-service groceries and the displacement of custom-made apparel and shoes by mass-produced ready-to-wear clothing.[3] The growth of the pharmaceutical manufacturing industry reflects two different types of substitution: the displacement of compounding in the retail establishment by a mass-production technology and the substitution of low-cost drug therapy for more costly types of therapy.

Usually the growth of pharmaceutical manufacturing in the 1940s and 1950s is attributed to the introduction of the new sulfa drugs and antibiotics since these were more difficult to manufacture than many older drugs. While the new products did in fact contribute to the change, the influence of general economic forces should not be dismissed. The pharmaceutical manufacturers also took over the production of dosage forms of virtually all the old drugs. Today, the retail pharmacist does virtually no compounding at all.

The substitution of drug therapy for other medical technologies has achieved significant economies, and the economies available from the greater use of drugs have grown as a result of recent large increases in the prices of other medical services. By contrast, the prices of drugs have remained stable. Their relative prices compared to those of other forms of therapy have declined, and it is the relative prices that are relevant in assessing the available economies. The increase in the use of medical services has also increased the potential savings from the substitution of drugs for medical services. But the development of drug therapy requires the discovery and development of new drugs.

The Need for New Drugs

Despite the medical contributions of the "wonder" drugs of the last three decades, new drugs are needed for the treatment, prevention, and cure of major diseases. A look at just a few categories of illnesses reveals the need for additional pharmaceutical research and the large potential contribution that can be made.

Infectious Diseases. Although the greatest pharmaceutical triumphs have been in the field of infectious diseases, much remains to be done. Antibiotics have greatly reduced mortality from pneumonia, meningitis, tuberculosis and septicemia, among other diseases. Nevertheless, infectious diseases taken together still account for 7 percent of all deaths [4] and a significant amount of severe disability. Furthermore, certain infectious diseases, once effectively treated with drugs, have reappeared in recent years. For example, in 1970 venereal disease was the most prevalent reported infectious disease, with over 2.8 million active cases. In part the problem has reappeared because the bacteria have become resistant to penicillin, which is now effective against gonorrhea only in very large doses. A more important factor, which is social rather than medical or bacteriological, is the permissive contemporary attitudes toward sex.[5]

Some currently important bacterial diseases are the paradoxical by-products of our therapeutic successes. For example, hospital gram-negative infections have now become a relatively common terminal disease for patients who are alive because of our success in treating their cancers or the injuries and burns they received in major accidents. The incidence of these infections has also increased as a result of the increase in the number of older people. The bacteria in question usually do not affect humans but do cause disease in these weakened patients. Unfortunately, the ability to treat gram-negative infections is still modest. New drugs not yet known are required.

Mental Illness. Recent statistics on mental illness show that major therapeutic advances have been made. New tranquilizers and anti-depressants helped reduce the number of patients in mental hospitals from 558,000 in 1955 to 339,000 in 1970. During those years the average hospital stay for mental illness dropped from eight years to one and a third years.[6] Tranquilizers and anti-depressants had the effect of decreasing the American mental hospital population by half compared to what it would otherwise have been. Mental illness, nevertheless, remains a serious burden. One estimate is that the total cost to the U.S. economy of alcoholism alone is $15 billion per year, consisting of $10 billion in lost work time, $2 billion in health and welfare services, and $3 billion in property damage and medical expenses. This estimate does not include losses from reduced life expectancy, traffic fatalities, and arrests.[7] New drugs are needed to help reduce this burden.

Cardiovascular Disease. Cardiovascular diseases are the leading cause of death in the United States, accounting for 53 percent of all deaths in 1968.[8] Part of the reason for this is the increase in the number of those over forty-five years of age—the most susceptible portion of the population.

Despite the rise in the proportion of older persons in the population, the annual death rate from cardiovascular disorders fell from 515.1 to 494.0 per 100,000 between 1960 and 1970.[9] Drugs doubtless were a factor in this decline. The major drugs now in use against this disease were first introduced in the late 1950s and early 1960s but few have been introduced since.

The reduction in the annual death rate from hypertensive heart disease and hypertension has even more dramatic; from 44.1 to 11.0 per 100,000 between 1958 and 1967. The great improvement is largely due to the use of anti-hypertensive drugs. Recently there has been a growing use of drug therapy to regulate abnormalities of lipid metabolism, and significant attention is now being given to the identification of the causes of atherosclerosis.

Arthritis. About 50 million persons suffer from arthritis to some degree. Approximately 17 million require medical care and 3.4 million are disabled.[10] Except for gout, the causes of arthritic diseases are unknown, and current treatment provides only symptomatic relief. The available drugs include steroid hormones and non-steroidal anti-inflammatory compounds such as phenylbutazone and indomethacin.

Cancer. New drugs are needed for cancer. With federal support, medical research has concentrated heavily on cancer and has succeeded in developing new drugs that have contributed to an increase in survival rates of patients with certain types of cancer. In 1967, less than one-fifth of all patients survived for five years after beginning treatment; by 1970 the five-year survival rate had risen to one-third. Drugs, however, cannot claim all of the credit; early cancer diagnosis and advances in surgery and radiology probably have been more important factors than drugs in the decline.

Viral Infections. Anti-viral drugs, although not of practical therapeutic use today, are clearly a promising field. The potential economic benefits arising from effective treatment of the common cold alone are enormous. Interferon, which is a natural substance induced in mammalian cells by exposure to a virus, inhibits the growth of the virus in the infected cells and prevents its appearance in neighboring cells. But formidable difficulties stand in the way of putting this knowledge to use in the development of a drug. Interferon is difficult to extract and appears to be effective only in the species from which it is obtained. Current efforts are directed toward seeking a drug that stimulates the production of interferon within the infected cells, rather than a method of extraction.

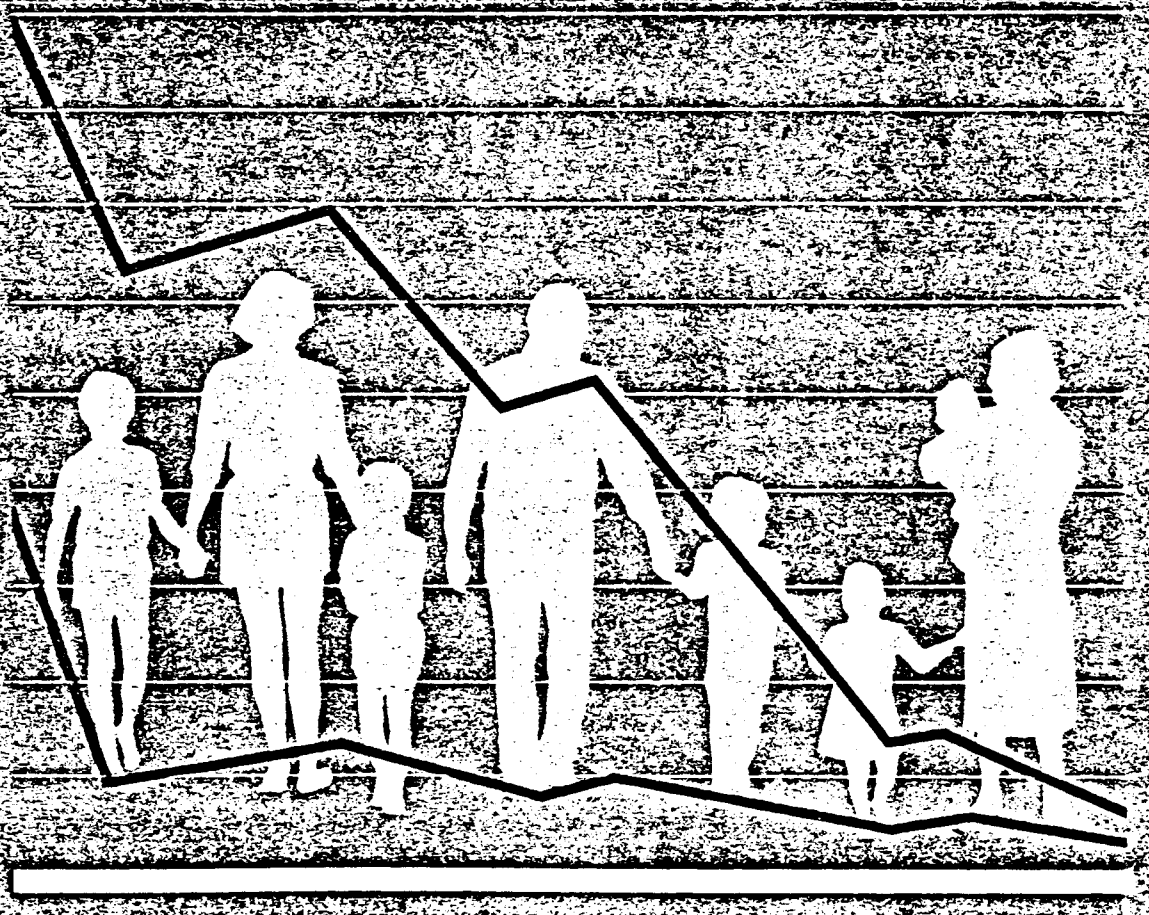
Can R&D Add to the Armamentarium?

Frequently the suggestion is made that additional R&D efforts are unlikely to be productive because the major discoveries of the 1940s and 1950s have exhausted the available opportunities. New discoveries, it is said, must await a major breakthrough of the magnitude of penicillin, and the prospect for a breakthrough of this magnitude is dim. On the contrary, many new drugs introduced since 1960 have proven to be therapeutically significant. Ampicillin has a wider antibacterial range than either penicillin G or penicillin V and destroys such penicillin-resistant, gram-negative organisms as Salmonella, Shigella, Haemophilus influenzae, and some species of Proteus. It is especially effective against urinary tract infections which generally involve gram-negative organisms. Cephalosporins, a family of relatively new wide-spectrum antibiotics, work against penicillinase-producing staphylococci and streptococci that resist older penicillins. Doxycycline, a new broad-spectrum antibiotic can be safely used by patients suffering from renal insufficiency, who risk serious side effects from the use of other tetracyclines. Other important new antibiotics include gentamicin and carbenicillin which are effective against severe infections caused by gram-negative organisms resistant to most other antibiotics.

In the cardiovascular field, the diuretic anti-hypertensive agent, chlorothiazide, which was introduced in the late 1950s, was a major therapeutic innovation, and a number of other anti-hypertensive drugs have been introduced. More recently, innovation has been slow, in part because the long-term use required of drugs such as these increases the risk of toxicity, which in turn has made FDA licensing especially restrictive. The importance of these new drugs is demonstrated by the fact that physicians have shifted to them rapidly and academic experts have endorsed them.

Tab 85

Vaccine Supply and Innovation



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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competencies and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of the appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under both the Academy's 1863 congressional charter responsibility to be an adviser to the federal government and its own initiative in identifying issues of medical care, research, and education.

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Over the past two decades, pharmaceutical companies have been withdrawing from vaccine manufacturing and marketing. Increasingly, the liability situation and its consequences (i.e., litigation costs or difficulty in obtaining insurance coverage) have been cited as major factors in the decision to withdraw. These decisions seem to indicate that present or anticipated vaccine-related injury liability expenses are seen as an unreasonable burden (or an unacceptably risky gamble) in relation to the costs of product development and the income from sales.

Manufacturers are apprehensive that without some means of compensation for unavoidable vaccine injury and temporally related conditions, the present unclear state of the law will continue to allow them to be held liable for such conditions and penalized financially.

The future behavior of the courts and the responses of the manufacturers cannot be predicted with certainty, but the committee is concerned that the apprehensions themselves might have a negative effect. Earlier withdrawals from the market have created a situation in which the United States is almost totally reliant on one manufacturer for polio and DTP vaccines (Lederle), and on another for measles, mumps, and rubella vaccines (Merck Sharp & Dohme). If apprehensions about the current unclear state of the law caused these manufacturers to withdraw, the vaccine supply and immunization programs could be jeopardized, leading to possible resurgence of these diseases. Also, the apprehensions discussed above are a disincentive to investment in the development of new (or improved) immunizing agents and to competition from new or foreign firms.

Proposals to remedy the compensation and liability problems connected with vaccine injury are discussed below.

A NATIONAL VACCINE COMMISSION

The lack of a formal mechanism to promote cooperation in the innovation, production, and use of vaccines limits the benefits obtainable from existing immunization programs and hampers the development of new programs. The problems associated with the absence of such a mechanism are primarily those of omission rather than commission: they include delay or inefficiency in achieving desired outcomes and failure to tackle problems for which no existing group has direct responsibility.

To overcome these difficulties, the committee recommends the establishment of a national vaccine commission. This commission would monitor all aspects of immunization efforts in the United States. One of its primary responsibilities would be early identification of potential problems affecting vaccine supply. It also would help to educate and inform the public, physicians, and government decision makers about the effects of various immunization actions and policies. When necessary, the commission would become an impartial broker to promote the availability of needed vaccines and to coordinate collaborative activities for which no suitable mechanism exists.