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Le journal canadien de chirurgie

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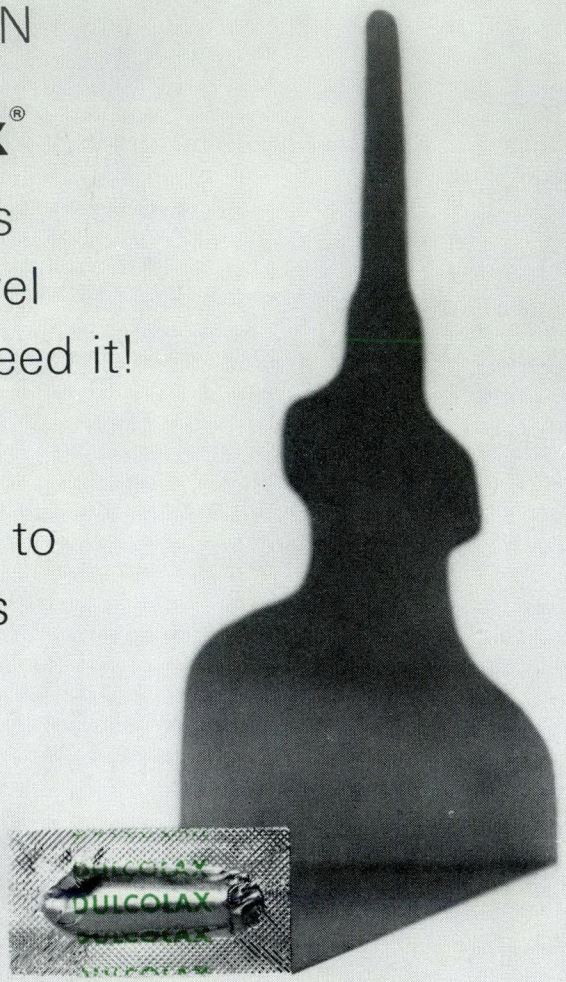

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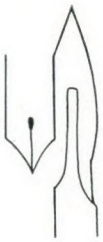

QUILL ON SCALPEL This section provides a medium through which Canadian surgeons can declare themselves, briefly and informally, on the day-to-day affairs of surgery.

FLAMMABLE FABRICS AND HUMAN BURNS*

Each year approximately 180,000 Canadians burn themselves;[1] about 600 of them die from their burns.[2] Between 30% and 40% of burns are caused by direct contact with flames,[3, 4] and these "flame" burns are responsible for the greatest number of burn deaths.[3-5] The ignition of clothing, the single most significant feature of flame burns,[5] is most common in the very young and the elderly[6] and produces the most severe burns.[7]

Flame burns are responsible for 31% of the burn admissions to the Hospital for Sick Children, Toronto. A review of 100 flame burns, five of which were fatal, revealed that clothing was ignited in 90%. In 17% of these, flammable fluids were involved, and so the flammability of clothing was not the primary factor in the burn injury. However, in 25% of these cases the small flame of a match or cigarette lighter ignited clothing and produced a major, and sometimes fatal, burn. Of these 25 children, 12 were burned by flaming nightgowns and pyjamas, five by shirts, four by dresses, two by pants, one by a blouse and one by a towel tied around the neck. In each case the child would not have been burned if the clothing had been non-flammable. In most flame burns only exposed areas of the body would be burned, or there might be no injury at all if the clothing did not ignite. Non-flammable clothing would prevent burns due to clothing ignition and also protect the wearer against flame and radiant heat burns. Flammable fabrics are also responsible for fires in bedding, draperies, and tents, all of which may cause human burns.[8]

Experience at the Hospital for Sick Children confirms the reports of others that most clothing burns are due to fabrics of normal flammability—85% of clothing worn in North America, chiefly cotton, falls into this category.[9, 10] The elimination of highly flammable clothing therefore has little effect on the overall incidence of clothing burns.[9] Cotton is responsible for clothing burns in 87% of cases, nylon in 7%, "synthetic" fibres in 3%, wool in 2% and cotton-Dacron combinations in 2%.[8] Fabrics with normal flammability can be made more flammable by changing the weight, weave and finish. Clothing that is loose and flaring or fabrics that are napped or piled burn faster. Synthetics may melt to form a burning syrup.[11] The afterglow of many fabrics produces more heat than the flame itself.[12] Thus it is difficult to produce entirely safe fabrics.

Flame-proof clothing can be produced from fabric made from non-flammable fibres or by processing normally flammable fabric to render it flame-proof. Many types of synthetic fibres are non-flammable or can be made non-flammable by introducing fire-resistant chemicals into the "melt" from which the fibres will be made.[9] Normally flammable fabrics can also be flame-proofed by weaving non-flammable synthetics into them. Cotton with 40% Modacrylic is flame-retardant.[13] However, because non-flammable synthetics have a less desirable texture and are more expensive they have not replaced normally flammable fabrics.

Normally flammable fabrics, mainly cotton, can be flame-proofed by the addition of various fire-resistant chemicals, the simplest of which is boracic acid.[14] Phos-

*This review, which was suggested by the Committee on Public Health of the Ontario Medical Association, was made possible by a grant from the Ontario Medical Foundation.

phorus-nitrogen resin and antimony oxide chlorinated paraffin finish[9] give more permanent flame-resistant finishes. However, many of these chemicals, such as boracic acid, wash out or dust out, and those that do not are expensive or damage the texture of the fabric.[1, 9]

Prevention of clothing burns can be approached from two directions: education of the public and legislation to force the industry to produce flame-proof clothing.

In Britain, flame-proof clothing has been marketed with appropriate labelling, yet, in spite of an education campaign to increase public awareness of the hazard of clothing burns, the public has refused to buy the slightly more expensive flame-proofed clothing and prefers to take a chance with cheaper flammable garments. To date no fully successful public education campaign has been mounted.[9, 15, 16]

Legislation prohibiting the sale of exceptionally flammable fabric has eliminated the almost explosive "torch sweaters" and the highly flammable cowboy chaps once sold in the United States,[9, 12] and, in Britain, flame-proofing has been made compulsory in children's nightdresses.[9, 17] This legislation has been a step in the right direction, but the normally flammable fabrics responsible for most clothing burns remain on the market. In addition, we do not have yet a laboratory test that will determine accurately which fabrics are "dangerous" and which are not.[9] Most fabrics now in use are dangerous not because of excessive flammability, but because of the wearer's carelessness. Finally, these fabrics play such a large part in our economy that legislation against them—to force the maker to produce more expensive, less attractive, flame-proofed fabrics—is probably not warranted at present.

The only Canadian law limiting the sale of flammable fabrics is the Hazardous Products Act, and it deals only vaguely with this subject. It states that "No person shall advertise, sell, or import into Canada a hazardous product . . . any product that is or contains a poisonous, toxic, *inflammable*, explosive, or corrosive product likely to be a danger to the health or safety of the public."[9] This law will prevent the sale of exceptionally flammable fabrics but will not control the use of normally flammable fabrics—the main offenders. Canada does not have any particularly common type of clothing burn such as the severe burns frequently suffered by little girls in Britain when their nightdresses are ignited by unguarded electrical fires.[17] Thus it is difficult to frame effective legislation, as Britain has been able to do, to reduce significantly clothing burns by controlling a specific type of clothing fire. It seems impractical legally to force all clothing to be flame-proofed.

The National Research Council of Canada continues (1) to collect data on burns to define better the flammable-fabric problem in the hope of finding some area where control will be possible, (2) to do research into better ways of testing the flammability of textiles, and (3) to survey the literature and new products to discover methods and products that might be used to lessen our fabric-burn problem.[18]

However, in the face of this negative survey, we still need much more public education regarding flammable-fabric burns. Individual citizens, if they were made sufficiently aware of the burn problem, might reduce fabric burns by avoiding situations where clothing may be ignited and by creating a demand for flame-proof fabric. This demand would encourage an already willing textile industry to produce better and cheaper non-flammable fabrics.

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LECTURE: RITUAL OR REALITY?

> "No lecturer can be sufficiently acquainted with the nature and causes of the transient hesitations and perplexities which beset the intellectual progress of any individual mind . . . (that he can) adapt his exposition closely to the intellectual needs of any individual. Besides, the one thing that the lecturer cannot allow is the pause for reflection; he must go on talking."[1]

According to Henry Sidgwick's "A Lecture Against Lecturing",[1] the expository lecture has limited usefulness. Sidgwick summarized his reservations at that time by saying "(if) the lecturer's function is merely to impart instruction by reading or saying a series of words that might be written and printed . . . this species of lecture is an unsuitable and uneconomical employment of the time of the teacher and the class". Yet, 80 years later, in most of our "scientific" meetings, we rely on this technique and thus demonstrate how little we have learned from earlier teachers. Men of international repute, acknowledged masters of content, rise before us often to read or disclaim haltingly; "It is – um – um – my intention to – ah – ah – speak to you today – about – um – um – the connection – er-ah – or I should say the relation between the pancreas and – ah – pineal – homeostasis."

To the critical listener such lectures as these seem not to have been prepared but to have been accumulated. The speaker's text has no (apparent) logical order and his slides (few or none of which were prepared professionally) cannot be read except from the first few rows. The resentment his listeners feel is almost palpable and, despite his eminence and their compulsion to hear the famous, many will leave before he is through.

Masters of content are not always (or not often) masters of form. Hence, these spectacular failures (and the waste of professional time and money they represent) will cease only when organizers of scientific meetings become tough-minded. Under our mythology, the program committee chairman feels unable to ask intended faculty for their credentials. However, if he is to do his full duty to the sponsors and to the consumer, he must consider not only the visitor's eminence as a scientist but his ability to present his material. In summary, unless we are prepared to abandon the lecture altogether, we must institute some sort of "quality control". At the recent 40th Annual Meeting of the Royal College of Physicians and Surgeons of Canada held in Ottawa, Dr. Helen E. Reid and her colleagues from the Hospital for Sick Children in Toronto showed, in their "Preview and Rehearsal Service", how this might be done.

J. O. Godden

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REVIEW ARTICLE

INTRAVENOUS HYPERALIMENTATION: A REVIEW*

JOEL B. FREEMAN, M.D. and LLOYD D. MacLEAN, M.D., F.R.C.S.[C], *Montreal, Que.*

PROTEIN hydrolysates have been used for at least 70 years as a source of intravenous nitrogen.[1, 2] General application of this technique has awaited the development of safer methods of cannulation of central veins, and the clinical and experimental demonstration that the technique can be life-saving. In 1967, Dudrick[3, 4] administered a 30% glucose-hydrolysate solution to four 12-week-old Beagle puppies, while four litter-mates were fed a standard diet. Over the following 255 days, all the puppies maintained exclusively on intravenous feedings outstripped the controls in weight gain and matched them in skeletal growth.

In 1968, Wilmore and Dudrick[5] described normal growth and development in an infant who had received all nutrients by vein for 44 days. Wilmore *et al.*[6] published a cumulative report of 18 infants similarly treated in 1969. Since that time, many other workers have demonstrated weight gain and positive nitrogen balance without oral intake in adults,[7-11] in patients with acute renal failure[12] and in infants[13-16] receiving this therapy.

This communication will review the theoretical and practical aspects of intravenous alimentation based on our experience over the past eight months at the Royal Victoria Hospital, Montreal, with 60 critically ill adult patients. We will present a summary of nitrogen balance and the rationale underlying the protein-hydrolysate-hypertonic glucose mixture. The mixing technique for both large and small hospitals will be discussed in detail, as well as the indications for treatment and the methods for avoiding complications. We will also describe our methods for managing patients with complications and those with special medical problems.

*From the Department of Surgery, Royal Victoria Hospital and McGill University, Montreal, Que.

Supported by a grant from the Medical Research Council of Canada.

INDICATIONS FOR INTRAVENOUS HYPERALIMENTATION

"The most destructive processes seen in the study of body composition are those that combine severe injury with starvation and invasive sepsis."[17]

In planning metabolic and nutritional care during acute illness, one must be aware of the caloric intake as well as the daily electrolyte balance. Any patient who consumes 2000 to 3000 cal./day in health should receive at least that much when he is attempting to heal a wound and/or ward off infection. It now appears that positive nitrogen balance with weight gain can be attained with parenteral nutrition alone.[7-11] Controlled studies have also shown that nutrients are as efficiently utilized when given by vein as when given by mouth.[18, 85] Therefore, intravenous alimentation is indicated in any patient who has a consistently demonstrable reduction in his caloric intake, especially when tube or oral feedings produce undesirable side effects.

An *absolute indication* for intravenous alimentation is found in patients who are unable to eat or in whom a malfunctioning gastrointestinal tract prevents adequate absorption of nutrients; e.g. those with coma, cerebrovascular accident, severe burns, sepsis or trauma, oral or pharyngeal cancer, gastrointestinal obstruction, severe enteritis, short-bowel syndrome, congenital abnormalities of the gastrointestinal tract, peritonitis, and anorexia nervosa.

A *relative indication* is provided by patients who can eat but who would benefit from temporary reduction of oral intake; e.g. those with any of the following: carcinomatosis; anorexia secondary to radiation or cancer chemotherapy; intestinal fistulas, especially those located in the small intestine; non-healing sacral decubiti; and preoperative malnutrition.

The necessity for preoperative preparation should be emphasized. Normal subjects maintained on a protein diet of 10

g./day and subsequently fed intravenously require 33% more protein to attain nitrogen balance than control subjects who are fed normally before intravenous feeding begins. Clinically, a patient may present in negative nitrogen balance with weight loss because of preoperative anxiety, pain, nausea, vomiting, anorexia or diarrhea. In addition, patients seldom eat adequately during the investigational period and their postoperative intake is seldom greater than 700 cal./day. If the patient develops some complication after operation, his poor nutrition will continue and the total period of inadequate intake may easily reach three weeks, with an approximate deficit of 20,000 calories. Even if the patient does have reserve fat, this cannot be converted to protein.

Practical Management

Subclavian venipuncture is performed as described by Dudrick and Wilmore[9] and Borja and Hinshaw.[19] Catheters placed through the brachial or axillary veins are dangerous for prolonged intravenous alimentation because there is little or no circulation between the peripheral vein wall and the catheter, and constant arm movement predisposes to phlebitis. Furthermore, the position of the catheter must be verified by radiograph because if it enters the external jugular vein or is accidentally pulled back, venous thrombosis may occur. The internal jugular approach assures that the catheter will lodge in a large-calibre vein,[20] but occlusive dressings are very difficult to maintain on the neck and restrict head movement, which is uncomfortable for prolonged periods.

The care and placement of the catheters must be meticulous. Dudrick's recommendations must be followed closely in order to prevent complications. We assign dressing changes to a specially trained nurse so that proper care is assured.

The most common complication, clotting of the catheter, is easily treated by adding heparin (one unit of heparin per millilitre of solution). Local infection is common but usually occurs in patients where this risk can be predicted. The factors predisposing to infection include the presence of other catheters, concomitant liver disease, the administration of broad-spectrum antibiotics, and prolonged illness or sepsis during which technique is often violated and resistance is low. While the incidence of bacterial sepsis has long been recognized,[21-23] Candida sepsis is an increasing hazard when catheters have been in place for more than 15 days.[24] In our experience, candidiasis seems to occur only in patients who are on broad-spectrum antibiotics during hyperalimentation.

Catheter sepsis can be prevented by substituting Teflon for polyvinylchloride catheters; by using millipore filters in the intravenous line;[25] by meticulous attention to mixing techniques and catheter care; and possibly by giving intravenous fats through a peripheral vein, when the risks of central catheterization are excessively high. Routine blood cultures and urinalysis should be done every seven days, with a special search for Candida.[24]

Other complications, while rare, are equally hazardous; these include pneumothorax, catheter embolism, air embolism and injury to the subclavian artery or brachial plexus. Hydrothorax results when the catheter is not properly placed in the lumen of the vein. Phlebitis of the upper thorax or neck can occur when the catheter lies in the cephalic or external jugular vein. Catheters that lie in the internal jugular vein are well tolerated, but patients must be carefully observed for neck pain or swelling. One must be thoroughly aware of all of these possibilities in order to avoid the serious sequels of unrecognized complications.[26-29] Catheter embolus can be prevented by using a plain catheter or a standard intercath from which the female adapter has been removed. After venipuncture, the needle is withdrawn over the catheter, which is then fitted with a blunt needle.

Water and Electrolytes

Routine Tests

The following orders should be written routinely at the beginning of therapy:

(1) Serum sodium, chloride, potassium, carbon dioxide combining power, blood urea nitrogen (BUN) and glucose—every Monday, Wednesday and Friday.

(2) Calcium, phosphorus, magnesium, protein electrophoresis, hemogram, prothrombin time and creatinine—every Monday.

(3) Daily weights; fractional urines (or Dextrostix) and temperature—every six hours.

(4) Serum osmolarities and urinary electrolytes—as indicated.

(5) Blood cultures for bacteria and fungi—every Monday. This blood must be drawn from a peripheral vein and not from the subclavian catheter. We believe that the accumulation of fibrin on the catheter tip may predispose to infection. Accordingly, the catheter is adjusted weekly and failure of blood to return promptly suggests that clot is present, and removal of the catheter should be seriously considered.

Rate and Infusion

Patients who do not have renal, cardiac or liver disease will tolerate 3000 to 4000 ml. of nutritional fluid a day. It is best to begin with a rate of 90 ml./hr. and gradually increase the flow to 140 ml./hr. over several days. This schedule will avoid hyperosmolarity and give the pancreas time to increase its output of insulin. The nursing staff should be provided with tables clearly showing the conversion of drops per minute into ml./hr., and 100-ml. drip chambers must be interposed between bottle and tubing. Above all, the nurses must understand that constant infusion is the primary objective and that, if the input should fall behind, the deficit is not to be corrected by rapid infusions over the last hour or two of the shift. Rather, errors in the rate should be recorded and the prescribed rate resumed.

Complications

Hyperglycemia.—Blood glucose levels of under 200 mg./100 ml. or glycosuria of less than 1% is not treated. When the infusion is constant and nursing care is good, hyperglycemia is uncommon. Glycosuria usually occurs only during the first 10 days of treatment and need arouse no concern unless it is accompanied by prerenal dehydration secondary to water diuresis. Two per cent (4+) glycosuria should be treated vigorously (12 to 20 units of crystalline zinc insulin subcutaneously) because one does not know how much greater than 2% the actual "spillage" is. A 2% spillage occurring twice in succession is sufficient evidence of significant glycosuria, if the physician is certain that the previously ordered insulin was given. Because of the variance in renal thresholds for glucose, blood Dextrostix determination may prove more accurate than fractional urines in the problem patient. Increasing the potassium concentration is another valuable way of increasing glucose utilization.[8] Because the normal pancreas can increase its output, do not give insulin routinely unless the patient has diabetes or is severely cachectic.

Hypoglycemia.—Circulating levels of insulin are continually elevated during intravenous alimentation because of pancreatic stimulation. Sudden cessation of the nutritional solution will result in hypoglycemia with a wide range of symptoms — from sweating and palpitation to central nervous system signs. Herein lies one of the principal reasons for administering routine plasma infusions through an alternative route, because if the plasma is given into the subclavian catheter, the nutritional solution will be temporarily omitted. When it is time to discontinue nutritional fluids, the bottle is replaced with 10% glucose which is run at 50 ml./hr. for a minimum of five hours. A similar procedure is followed when a patient on nutritional solutions is to have an operation.

Hyponatremia. — Hyponatremia is very common during hyperalimentation, and levels of 130 mEq./l. are frequently seen and require no treatment. When the level is below 130 mEq./l., the serum glucose should be checked because when it is elevated, it tends to increase intravascular water.[30] Thus, hyponatremia may effectively be treated by insulin and/or potassium.

When not due to hyperglycemia, hyponatremia in the critically ill patient is usually associated with cardiac, hepatic or renal disease. These patients may not

tolerate more than two bottles of nutritional solution a day and when hyponatremia occurs, it usually responds to water restriction. Reducing the rate of nutritional fluids to 40 ml./hr. will often raise the serum sodium. For more serious deviations of electrolyte values, the nutritional solutions should be withdrawn temporarily and 10% glucose substituted.

Occasionally, hyponatremia may be due to an absolute sodium deficit. This usually occurs in seriously ill patients who are sustaining large urinary and intestinal losses and have received inadequate and/or inappropriate replacement. Since the urinary excretion of sodium is diurinal, the last urine collection of any 24-hour period may not be a representative aliquot for electrolyte determinations. Therefore, the entire 24-hour collection must be saved and adequately mixed and measured before sending a sample to the laboratory.

Hypernatremia.—Hypernatremia is usually secondary to the prerenal azotemia that follows an excessive water diuresis. Blood urea nitrogen is also raised but the creatinine is normal. If hypernatremia is accompanied by lethargy, hyperventilation or coma, the syndrome of hyperosmotic non-ketotic diabetic acidosis should be considered and verified by appropriate tests.[31] Hypertonic solutions are thought to shift fluid from the intracellular to the extracellular space and thereby dilute serum bicarbonate.[32, 33] Accordingly, a lowered carbon dioxide combining power may be the first sign of an impending hypertonic acidosis. Such acidosis occurs more commonly in infants, and when seen in adults is usually associated with excessive infusion rates. If the intravenous tubing is inadvertently unclamped the patient may receive 1100 ml. of hypertonic fluid (1300 mOsm/kg.). Therefore, unless a constant infusion pump is being used, intravenous tubings (pedatrols) containing a 100-ml. calibrated chamber* are used, thereby limiting the size of an inadvertently administered bolus of fluid to the amount contained in the chamber. Sixty drops from the chamber equal 1 ml. Two clamps are placed between the pedatrols and the bottle, and released every hour to permit the appropriate amount of fluid to enter the pedatrols.

*Soluset-100. Abbott Laboratories, North Chicago, Ill. 60064.

Chloride

Theoretically, hyperchloremia could occur when both sodium and potassium are administered as the chloride salts. In practice, this is seldom a problem. If it should occur, sodium may be given as the bicarbonate salt or potassium may be given as the phosphate salt.

Allergic Reactions

These are uncommon and usually abate when the infusion is discontinued, 10% glucose is substituted and antihistamines are administered.[31] If a reaction occurs a second time, a different hydrolysate must be tried.

Fever

Whenever a patient has an undiagnosed fever, the following steps should be taken: (1) blood cultures should be drawn from a peripheral vein and from the subclavian catheter for bacteriology and mycology; (2) the solution should be discontinued and 10% glucose substituted. Ten millilitres of the original solution should also be sent to bacteriology and mycology; (3) if the cause of the fever is not established after 24 hours, the catheter should be removed and similarly cultured, even though previous blood cultures have been negative.

As mentioned previously, Candida septicemia may be asymptomatic in its early stages.[24] Therefore, routine urine and blood cultures for mycology should be done once a week and more frequently if the patient has an unremitting low-grade temperature, which continues after hyperalimentation has been discontinued.

Conversion to Oral Intake

If the usual criteria for oral intake are met, patients on nutritional alimentation may eat at any time. Because of their high glucose concentrations, the solutions may

decrease appetite. Accordingly, the infusion rate is gradually decreased while oral intake is increased—as measured by accurate calorie counts. The catheter must not be removed at the onset of oral intake, because many chronically ill patients will eat no more than 900 cal./day for several days or even weeks and may require intravenous supplementation. If the patient is able to consume 1500 cal./day while receiving one bottle of nutritional solution, the catheter may be removed after four to six hours of a 10% glucose infusion.

Marginal oral intakes may be satisfactorily supplemented with high-caloric high-protein milkshakes. The high caloric value of these drinks (1 cal./ml.) invokes an unavoidably high osmolarity and fat content accounting, in part, for the diarrhea which sometimes accompanies early feedings. Mucosal atrophy and loss of the absorptive function of the gastrointestinal tract occur with chronic starvation,[34-36] and diarrhea may be partially circumvented by administering frequent small feedings during the first days of oral intake. The use of a chemically defined diet* is theoretically appealing, but our limited experience with this product does not permit comment.

Intravenous Feeding for the Critically Ill Patient

Heart failure.—Heart failure seriously restricts the volume of fluids that can be administered each day. Two bottles of nutritional solution (about 2200 ml.) provide adequate maintenance but less will not. These patients may not be able to tolerate this much fluid, but substitution of albumin infusions for plasma may raise the serum protein enough so that the patient can eliminate the excess water. If not, parenteral diuretics are administered until the patient can tolerate the required two bottles a day.

Renal failure.—Protein is not given parenterally to patients with renal failure because this might further elevate the BUN. Their chronic negative nitrogen balance is further accentuated by repeated dialysis, anorexia, the necessity for fluid restriction and a urinary nitrogen loss of at least 4 g./day. Administration of 50% glucose provides a maximal number of calories (about 2000 cal./day) in a minimal quantity of fluid to a patient consuming little or nothing by mouth but fails to provide nitrogen.[37] It has been shown, however, that an adult requires a minimum of 2 g. of essential l-amino acids per day.[38] When these amino acids are given along with an adequate number of calories, negative nitrogen balance will be avoided (although no weight gain will take place). Further experiments performed with variants of this diet led to an important observation, *viz.* if any other source of nitrogen was given in addition to the 2 g. of essential amino acids and carbohydrate calories, the patient went into *positive* nitrogen balance and gained weight.[39] The extra sources of nitrogen include ammonium chloride, glycine, glutamic acid and urea.

Contrary to popular opinion, urea is a valuable endogenous source of protein.[40] This has been repeatedly confirmed by the presence of radioactive nitrogen in body protein after the administration of ^{15}N-labelled urea. Since non-uremic subjects require 2 g. of essential amino acids, calories and any other source of nitrogen for weight gain and positive nitrogen balance, patients with renal failure can utilize their own BUN in attaining positive nitrogen balance, when given only 2 g. of essential amino acids and a source of adequate calories. Utilization of the BUN also reduces the frequency of dialysis and the severity of nausea, vomiting, pruritus and other such uremic symptoms. As the BUN approaches normal levels,* the nitrogen balance will again become negative unless the physician administers an exogenous source of nitrogen.

This essential-amino-acid (Giovannetti) diet has been used extensively on medical

*Vivonex. Vivonex Corporation, 876 West Dana St., Mountain View, Calif.

*If the serum creatinine does not remain stable, the falling BUN could be equally attributable to the diet or to an improvement in the renal pathology.

wards where many of the patients are able to consume food by mouth. Trauma, ileus, uremic enteritis and small bowel fistulas frequently preclude oral feeding in surgical patients with renal failure, especially when the renal failure is acute. Dudrick postulated that such a patient could receive these amino acids intravenously. He prepared a sterile essential-l-amino-acid solution using standard millipore techniques for sterilization.[12] This solution was mixed with hypertonic glucose (50%) and the final mixture was infused at a constant rate through a subclavian catheter. Following Dudrick's techniques, we have also produced a sterile amino-acid hypertonic-glucose solution which has proved safe in dogs and is now receiving a clinical trial.

In summary, azotemic patients are in severe protein and caloric depletion. Like non-azotemic patients they require a minimum of 2 g. of essential amino acids, an adequate number of calories and any other exogenous or endogenous source of nitrogen. In uremia, the patient's own BUN provides such a source. When given by mouth, this diet is effective. Reports on the efficacy of intravenous essential amino acids are encouraging, although no definite conclusions can be drawn from the few reported cases.

If the physician cannot produce his own essential-amino-acid mixtures, he should give 50% glucose in the usual manner and follow renal function daily. When the BUN has stabilized, small quantities of protein hydrolysates (50 to 100 ml.) are added daily and further treatment is based on the response observed. Even if the patient has severe oliguria, he must receive at least 20 to 30 mEq. of potassium each day.

Liver failure.—Glucose reportedly stimulates the combination of ammonia with glutamic acid and lowers the blood ammonia.[41] It is known that patients with liver disease given adequate calories orally will maintain nitrogen equilibrium or a slight positive nitrogen balance on 50 g. of dietary protein daily.[42] Although Schiff, in his monograph, states that intravenous glucose and protein hydrolysates can be given to patients with severe liver disease, he does not state how many grams of protein can be given.[43] We have had a limited experience with four patients suffering from advanced liver disease, two of whom were comatose. Of the 24-hour fluid requirement, 90% is given as hypertonic (40%) glucose and the remainder as protein hydrolysate. If no changes in the BUN, urea, blood ammonia or neurologic status occur, more protein hydrolysate is substituted for glucose until the conventional 750-350 mixture is attained.

There is a sound physiologic explanation for the somewhat surprising success of this treatment. Ammonia is formed by the breakdown of dietary nitrogenous substances in the gut. It is transported via the portal vein to the liver. Here ammonia is converted to urea by the ornithine-citrulline-arginine (Krebs'-Henselect) cycle.[44] A hepatectomy or an Eck's fistula will raise the blood ammonia in dogs. Feeding the animals protein will produce rapid hepatic coma. In the presence of protein or blood in the gut, similar elevations of blood ammonia occur in human cirrhotics provided bacteria are present to form ammonia. We postulate that the administration of intravenous protein is tolerated because the gut is bypassed. The precipitation of hepatic coma after the parenteral administration of ammonium chloride does not support this postulate.

The frequency of glycosuria does not appear to be increased when liver patients are treated with hypertonic glucose. Theoretically, fructose is a better sugar than glucose. However, the most highly concentrated fructose solution that is commercially available is only 10%, so that one would have to give huge volumes of fluid to administer sufficient calories.

Hyperalimentation Control and Ordering System

Ideally, one physician should supervise all subclavian venipunctures, write the initial routine orders, see the patients daily and continuously educate nurses and physicians in this potentially dangerous technique.

Co-operation from the hospital pharmacy is essential and the physician in charge of the program must teach the pharmacists the proper technique for mixing.

ROYAL VICTORIA HOSPITAL MONTREAL 112 QUEBEC

Addressograph

Nutritional I.V. Order Form.

Note: This form MUST be accurately filled out by the House Officer or Attending M.D. and the copy sent to Pharmacy by 10.00 a.m. each weekday, the original must be placed in the I&O section of the patient's chart. NO SOLUTIONS WILL BE MADE DURING WEEKENDS SO A THREE DAYS SUPPLY MUST BE ORDERED ON FRIDAYS.

AMINOSOL contains 23 mEq of Sodium
10 mEq of Chloride per
17 mEq of Potassium liter

	BOTTLE #1	BOTTLE #2	BOTTLE #3	BOTTLE #4
Aminosol	750 cc	750 cc	750 cc	cc
50% Glucose	350 cc	350 cc	350 cc	cc
Sod. Chloride (NaCl)	30 mEq	30 mEq	20 mEq	mEq
Pot. Chloride (KCl)	40 mEq	40 mEq	20 mEq	mEq
Pot. Phosphate (K2HPO4) 30 mEq/10 cc	5 mEq	5 mEq	5 mEq	mEq
Sod. Bicarbonate (NaHCO3) 5% soln. 10 mEq/50 cc	mEq	mEq	mEq	mEq
Calcium Gluconate 10% 5 mEq/10 cc	2 mEq	2 mEq	1 mEq	mEq
Mag. Sulphate 50% 4 mEq/cc	4 mEq	2 mEq	2 mEq	mEq
M.V.I. (10 cc per day)	3.3 cc	3.3 cc	3.3 cc	cc
Vit. K. (10 mgm every Monday)	10 mg			
Folic Acid(10 mgm every Monday)	10 mg			
Vit. B-12 (100 mgm every month)	100 mcgm			

Signature _____ M.D.
Date to be given _____
Filled by _____ Pharmacist
Date Mixed _____

Fig. 1.—A nutritional intravenous order for three bottles of hyperalimentation fluid for a single patient for a single day. This form is filled out and delivered to the pharmacy by 10 a.m. The mixed solutions are placed in the ward refrigerator by 4 p.m. and are given to the patient beginning at 8 a.m. the next morning.

After being guided in the ordering of nutritional solutions for the first day or two, the doctor in charge of the patient orders the solutions directly from the pharmacy. A sample of a typical order form is shown in Fig. 1. Because house staff rotate, new interns may make errors in ordering. The physician in charge should routinely check the order sheets and ask the pharmacy to report gross irregularities in prescriptions for nutritional solutions.

Improvements in Present Techniques

Millipore Filters

Each drop of fluid that leaves an intravenous bottle must be replaced by an equal volume of room air. Both room air and accidental contamination during mixing may introduce bacteria into the solution. To prevent this, we now place a millipore filter, a thin porous sheet of pure, cellulose esters,* inside a plastic Swinnex filter holder, which has male and female adapters to connect to any intravenous line and its corresponding catheter. A .45 μ filter will prevent the passage of all bacteria (except for some strains of pleomorphic Pseudomonas). The gravitational pressure from a simple intravenous fluid bottle will force flow through a .45 μ filter. A .22 μ filter will provide absolute sterility, but flow must be forced by a constant infusion pump.*

Constant Infusion Pumps

Although a large number of infusion pumps are commercially available, we have had experience with only three. The Harvard peristaltic pump employed by Dudrick in his animal experiments is excellent but expensive. The Holter infusion pump† is inexpensive, reliable over months of continuous use, portable, can carry a charge so that it can be transported with the patient and can serve two patients at the same time. The makers have proposed several important modifications to this pump and the new model will soon be released. The Baxter stroke volume pump has been tested here, but is still in the design stage. The intravenous tubing that accompanies this pump will contain a convenient bacterial and air filter.

Non-Reactive Catheters

Silastic is practically non-reactive when implanted into the subcutaneous tissues. Hence Silastic catheters are associated with less infection than polyvinylchloride catheters.[45, 46] At this time Silastic is expensive and is not supplied in a radio-opaque form. If the tip of one of these should break off and be carried as an embolus, it would be extremely difficult to locate. Teflon catheters are not only well tolerated by tissues, but are supplied in a radio-opaque form. Preliminary studies during routine intravenous treatment on patients in our surgical wards suggest that phlebitis is less frequent with Teflon than polyvinylchloride catheters.

*Millipore of Canada, Ltd., 55 Montpellier Blvd., Montreal, Que.

*Our more recent studies indicate that these filters may predispose to bacteremia.

†Model RDO 74. Brent Surgical, Toronto, and Extracorporeal Medical Specialists, Mt. Laurel Township, N.J.

Intravenous Hyperalimentation: Electrolyte Metabolism and Mixing Techniques

Nitrogen Balance

Nitrogen balance, a concept introduced in early studies on nutrition, refers to the difference between total nitrogen intake and total nitrogen excretion.[47] A positive balance generally reflects growth or repletion; a negative balance decay or depletion. A simple correlation exists between average daily weight gain and nitrogen retention, provided the nitrogen is being used—as evidenced by a stable BUN, serum creatinine and uric acid, and that the weight gain is not due to water retention—as evidenced by a zero water and sodium balance. In the absence of adequate calories, tissue nitrogen is mobilized and used in gluconeogenesis, releasing nitrogen which is then excreted. This internal mobilization occurs even if exogenous nitrogen is given, unless this nitrogen is accompanied by sufficient calories to render gluconeogenesis unnecessary. While several classical studies have invoked an obligatory nitrogen deficit after stress or trauma,[48, 49] we now know that nitrogen deficits can be reduced or even eliminated if nutritional intake is maintained during the post-traumatic period.[7-11]

One pound of lean body tissue contains 15 g. of nitrogen.[50] Simple operations or starvation will produce a loss of 10 to 15 g. of nitrogen per day in the absence of exogenous calories or nitrogen.[51] The provision of 750 cal./day reduces daily nitrogen losses to 8 g./day, but further caloric increments have no effect on nitrogen balance.[52] However, if both calories *and* nitrogen are supplied, the calories are used solely for energy while the nitrogen is used to produce new protein for intracellular synthesis. The minimum ratio of non-protein calories to nitrogen, in grams, is 150:1 (Fig. 2).

A 70-kg. man has approximately 500 g. as carbohydrate stores, a quantity insufficient to meet even a single day of fasting. Such a patient will use labile fat and protein over the first few days of fasting if during this time he receives only 600 cal./day in the form of 5% glucose. Since he needs approximately 2000 cal./day for maintenance, he will break down tissue protein to provide additional energy. Although patients seem to tolerate inadequate nutritional intake for three to five days, it is difficult to accept that even this short period of starvation is without detriment. If complications ensue, the patient will be less resistant to infection and stress because of this deficit.[53]

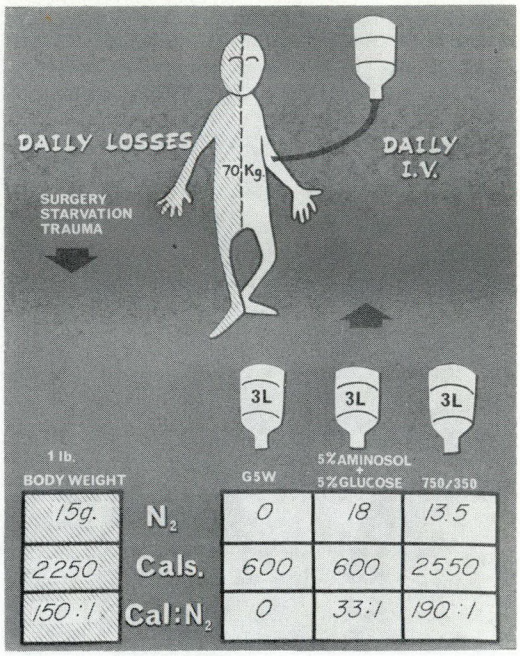

Fig. 2.—The nutritional benefits of glucose, Aminosol with 5% glucose, and Aminosol with 50% glucose are shown in the white blocks; the average daily losses they must replace are shown in the shaded blocks.

Protein Hydrolysates as a Source of Intravenous Nitrogen

The body acquires amino acids either by intestinal digestion of proteins or by intracellular transamination. An alpha-keto acid is converted to its corresponding amino acid by the transfer of an NH_2 group from the amino-acid pool. Any amino acid needed for protein synthesis can be manufactured if the body has the necessary transaminase enzyme and the appropriate alpha-keto acid, but in eight (essential) amino acids the body cannot synthesize the alpha-keto acid counterpart. Hence, these amino acids must be supplied in the

diet. Essential and non-essential amino acids have equally important roles in body metabolism.

Polypeptides, tripeptides and dipeptides are normally broken down by pancreatic enzymes located in the small bowel. Before they are given intravenously, proteins must be artificially hydrolyzed into amino acids and these amino acids must be in the levorotatory (l) form.* Amigen is a partial pancreatic enzymatic hydrolysate of casein; Aminosol is a hydrochloric acid hydrolysate of fibrin. Complete acid or enzymatic hydrolysis will destroy tryptophane and occasionally cystine,[54] both of which are essential amino acids which the body cannot manufacture.

Monopeptides are the only nitrogenous products that the body can use when given intravenously. Therefore, the dipeptides contained in *partial* hydrolysates are excreted in the urine. If mixtures of essential l-amino acids are administered, this peptide loss would be avoided.[55] In addition, there is evidence that the presence of non-essential amino acids in parenteral feedings inhibits the utilization of the essential amino acids.[56] The use of an essential l-amino-acid mixture, which contains no peptides, would eliminate the problem of urinary nitrogen loss. Crystalline amino-acid solutions have been safely administered by Wilmore and Dudrick[12] and are currently being investigated by a large North American pharmaceutical manufacturer.[57]

Sources of Calories

Carbohydrates

Attempts to find a substitute for glucose have centred mainly around fructose, used alone or mixed with an equal amount of glucose (invert sugar), and there is considerable evidence that fructose or invert sugar may be metabolically superior to glucose alone.[58-60] Fructose is phosphorylated to fructose 6-phosphate by fructokinase and then enters the Krebs' cycle. Fructokinase is less dependent on normal liver function than glucokinase, the analogous phosphorylating enzyme for glucose, which may account for the superior metabolism of fructose in the presence of postoperative stress, diabetes or liver disease.[61] Unfortunately fructose is available commercially only as a 10% solution and hence the volumes required to maintain caloric balance by intravenous alimentation would be enormous; i.e. 1 l. would contain 100 g. of fructose or 400 calories.

Glycerol is tolerated intravenously but has shown no superiority to glucose.[62] Like fructose metabolism, citrate metabolism is not altered in the postoperative state and, for this reason, citrate has been suggested as a glucose substitute.[63] Alcohol not only provides 7 cal./g., but also produces sedation, analgesia, and, in contrast to other analgesics, respiratory stimulation. (The potential hepatotoxic effects of intravenous alcohol given over long periods have not been evaluated.)

Fat is made soluble for intravenous use by the addition of an emulsifying agent to a triglyceride oil. Glucose is added to produce the required tonicity. This preparation provides 9 cal./g. but such side-effects as fever, hypotension, coagulation disorders, lipemia and a fat embolism-like syndrome have halted the use of such preparations as are available on this continent.[64-66] However, a soy-bean oil emulsion* that has been used extensively in Scotland[18, 67] and Sweden[68] is currently being investigated here and in the United States.[69] (Much of the earlier work on intravenous fats has been extensively reviewed elsewhere.[70])

In summary, several compounds are potentially capable of supplying the needed calories, but glucose is the safest agent now used for intravenous alimentation.

Basic Formula

To prevent catabolism, both nitrogen and calories must be provided. Since the maintenance of protein stores requires a

*The nitrogen radical of each of the body's 21 principal amino acids has the same spatial relationship to its alpha-carbon (the carbon atom directly adjacent to the carboxyl group) as l-alanine—the simplest amino acid. Hence the term "alpha l-amino acid".

*Intralipid. Pharmacia (Canada) Limited, Montreal 351, Que.

minimum of 1 g./kg., a 70-kg. man needs 70 g. of protein or 12 g. of nitrogen (16% of 70) per day.[71] One litre of 5% Aminosol in 5% glucose contains 50 g. of protein (6 g. of nitrogen*) plus 50 g. of glucose, and 750 ml. of this solution will provide 37.5 g. of protein or 4.5 g. of utilizable nitrogen plus 37.5 g. of glucose. To prevent gluconeogenesis, this 4.5 g. of nitrogen must be accompanied by 675 calories (4.5 x 150). The solution already provides 37.5 g. of glucose (140 calories) and the addition of another 350 ml. of 50% glucose will complete the 175 g. of glucose (700 calories), giving a nitrogen:calorie ratio of 1:190.

This mixture—750 ml. of hydrolysate plus 350 ml. of 50% glucose—contains 1100 ml. of water, 37.5 g. of protein, 4.5 g. of alpha-amino nitrogen, 212.5 g. of glucose (850 calories), 17 mEq. of sodium, 7 mEq. of chlorine and 13 mEq. of potassium.

Mixing Techniques

Whether the mixing system is open or closed, contamination may occur at any time. Filtered, non-turbulent air from a laminar air-flow hood provides a larger margin of safety[72] and allows the pharmacist to work with several bottles at the same time (Fig. 3). Although closed systems without laminar air have been used successfully, we believe that the initial cost and minimal operating expenses make the purchase of such a hood well worth while. Whether or not a hood is used, care must be exercised to assure that mixing is done in a room which is completely free of air turbulence, away from windows and working personnel.[84]

Casein hydrolysates are supplied in vacuum bottles. Solutions that are transferred by intravenous tubing run very slowly and therefore we have employed a 2000-ml. plastic bag.† The inlet tube of the bag is placed into a bottle of Amigen

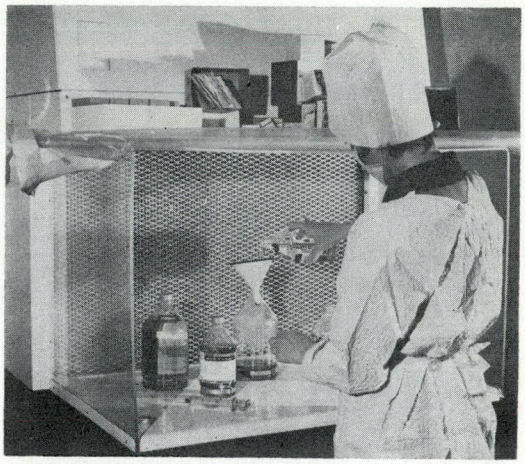

Fig. 3.—Aminosol and 50% glucose are being mixed in a laminar air-flow hood by a pharmacist observing sterile technique.

inside the hood and 1500 ml. of the solutions is transferred. Meanwhile, all of the additives are placed into a 500-ml. bottle of 50% glucose which is then similarly transferred. An additional 200 ml. of 50% glucose is added and the inlet tubing of the bag is tied with three knots. The completed mixture contains 1500 ml. of Amigen, 750 ml. of 50% glucose and about 100 ml. of additives, as electrolytes and vitamins.

Fibrin hydrolysates are supplied in screw-cap non-vacuum bottles. Using a large laminar air-flow hood, 250 ml. of Aminosol is poured from a 1000-ml. bottle into a second sterile empty bottle. This 250 ml. is replaced with 350 ml. of 50% glucose. The use of a sterile funnel permits rapid pouring. Recently, a solution mixing set* has been manufactured which forms a sterile junction between a 1000-ml. bottle of Aminosol and a 500-ml. bottle of 50% glucose.[73] Complete mixing of the two bottles is attained with five inversions and the 1500-ml. mixture contains a nitrogen: calorie ratio identical to that attained with the 750:350 mixture. With the exception of the time during which the bottle cap is removed and replaced with the mixing set, the mixing is done in a completely closed system. However, this still does not

*The 50 g. of protein in a litre of Aminosol theoretically contains 8 g. of nitrogen. However, 2 g. of these 8 g. of nitrogen are in the form of non-utilizable dipeptides and tripeptides. Hence, the statement that a litre of Aminosol contains 6 g. not 8 g. of nitrogen.

†TA-20 Fenwal Transfer Pack, Code No. 4R2041.

*No. 8100. Abbott Laboratories, North Chicago, Ill.

solve the problem of placement of the additives.

The bag system is preferable for the preparation of small quantities of solution because it is a closed system and, if proper precautions are taken, the solutions can be mixed without a laminar flow hood. In addition, no air enters the bag, which collapses under atmospheric pressure as it empties, whereas air must enter a bottle if flow is to continue. When large quantities of solutions must be prepared, the time saved with open-bottle mixing more than offsets this theoretical objection.

Additives

Additives are prescribed just as they are for routine intravenous therapy. The patient's losses are calculated, based on serum values, insensible, urinary and other fluid losses. The total electrolyte requirements are distributed equally among the bottles for the day, this being particularly important with potassium.

Sodium Chloride

The use of a concentrated sodium chloride solution* not only reduces mixing time, but is more accurate. Twenty to 40 mEq. of sodium chloride is added to each bottle for maintenance and more is added to compensate for other losses.

Potassium

Muscle contains 75% of the total body potassium and in the fasting state the potassium:nitrogen ratio in muscle is identical to the urinary potassium:nitrogen ratio. This observation implies that when cellular protein is broken down for gluconeogenesis, potassium is shifted to the extracellular compartment and then excreted. Therefore, potassium and protein deficits often coexist. When the physician begins to administer intravenous protein, he must supply potassium in the ratio of 5 mEq. for each gram of nitrogen, and in severe malnutrition this ratio may often reach 15:1.[74] When given to potassium-depleted rats, protein hydrolysates will not promote growth, and the addition of potassium results in growth with improved nitrogen balance; there is evidence of a similar relationship in man.[75] Accordingly, potassium requirements will range from a minimum of 80 mEq. to a maximum of 160 mEq./day. Even patients with oliguria require 30 mEq./day.

Calcium and Phosphorus

Calcium is lost in both the urine and feces. Patients on intravenous therapy lose nothing through the intestine unless they have a coexisting fistula, but immobilization increases urinary losses. Most patients remain in balance if they ingest 1 g./day by mouth,[76] and our preliminary calcium balance studies indicate that this will be sufficient during intravenous feeding as well. Ten millilitres of a 10% calcium gluconate solution contains one gram (4.74 mEq.) of calcium.

Phosphorus not only is important in bone metabolism, but also plays a central role in the transformation and production of high-energy compounds. We have very little data on phosphorus requirements because phosphate deficiency is rare, but the recommended dose is 1½ times the calcium dose[76]—roughly 15 mEq./day. This element is supplied by Travenol* as the monobasic potassium salt.

Magnesium

The body requires magnesium to activate a great many enzyme systems, particularly those concerned with oxidative phosphorylation. It is primarily an intracellular ion and there are no conclusive data on normal requirements. Based upon balance studies, 250 mg. of magnesium per day appears adequate for adults.[71] Since magnesium deficiency is most common in prolonged starvation or intravenous feeding, we have given 500 to 1000 mg./day. Two millilitres of a 50% magnesium sulfate solution contain 1000 mg. of magnesium (8.1 mEq.).

*23.4% sodium chloride containing 4 mEq./ml. Cutter Laboratories, Calgary, Alta.

*Baxter Laboratories of Canada Limited, Malton, Ont.

Iron

Parenteral iron gives rise to many undesirable side effects and should be administered only if serum iron levels are reduced. To avoid iron overload, do not give it routinely. Small daily maintenance doses can be given intravenously in dogs, but the deep intramuscular route is used in patients. Information on the most suitable preparations, doses and methods of injection is readily available.[78]

Trace Elements

This term applies to the remaining elements which function in all biologic systems and includes aluminum, cobalt, copper, manganese, zinc and at least 20 others. Because the measurement of these elements is still not routine, very little is known concerning the significance of alterations in their serum levels.

Zinc

Zinc is important in wound healing.[79-81] Zinc deficiencies arise because we constantly excrete 0.4 mg./day regardless of intake or urinary volume. Most students of long-term parenteral nutrition believe that one unit of plasma given twice a week will provide all the trace elements and the essential fatty acids. Proof of this assumption awaits further investigations.

Vitamins

The majority of commercially available parenteral preparations do not contain the fat-soluble vitamins. Although most vitamin-deficiency states are due to the lack of water-soluble vitamins, *single* vitamin-deficiency states seldom occur.[82] It is also possible that relative deficiencies may exist without clinical manifestation; this is especially true for vitamin A, which is important in wound healing.[83]

The contents of one 10-ml. vial of M.V.I.* will provide two to 10 times the National Research Council's recommended daily dose of each vitamin. This vial is distributed between the total number of bottles for the day.

A number of accessory vitamins such as choline, biotin and para-aminobenzoic acid are not yet available for intravenous use. However, folic acid, vitamin K and vitamin B_{12} are available in separate vials and should be administered when total parenteral nutrition continues for one week or more. There is, to date, no way of knowing whether these vitamins should be divided and given in small daily doses or given once weekly. We give 10 mg. of vitamin K and folic acid in the solutions every Monday. Although the body stores enough vitamin B_{12} to last for two to three years, 100 μg. are given in the solutions on the first day of treatment and once a month, to ensure that the weekly administration of folic acid does not mask a previously unrecognized pernicious anemia.

Summary and Conclusions

Intravenous hyperalimentation, a new form of therapy, is especially useful in patients who have gastrointestinal complications, notably fistulas and chronic peritonitis, and in preparing debilitated patients for definitive surgery. Recent experience at the Royal Victoria Hospital, Montreal, suggests that many lives can be saved with this technique, but it requires meticulous attention to detail if serious complications are to be avoided. This review outlines in detail the steps necessary to avoid complications and obtain adequate results. There is no value in giving less than a full regimen or in feeding the patient in an uncontrolled fashion. In the future this form of hyperalimentation, which requires a central catheter for long periods, will be supplanted in patients with a high risk of sepsis by feedings with intravenous fat and protein hydrolysates which can be administered into a peripheral vein.

Several workers have asserted that many patients would benefit if all periods of negative nitrogen balance were eliminated even after routine operation. This awaits further study, but it appears that many patients who have "uncomplicated" operations frequently have periods of prolonged recovery. Measurements of efficiency such

*Multiple Vitamin Infusion. Arlington Laboratories, USV Pharmaceuticals of Canada, Montreal 379, Que.

as postoperative oxygen consumption and the ability to exercise might provide the quantitative data needed to support this impression. It is now clearly documented that recovery from operation is associated with the ability to do more work with less cardiac output and less energy expenditure. It would be interesting to determine if this recovery process could be altered by the avoidance of a negative nitrogen balance.

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Résumé

Les auteurs, se basant sur leur expérience personnelle chez 60 malades très gravement atteints qui étaient hospitalisés à l'Hôpital Royal Victoria, exposent en détail les aspects théoriques et pratiques de l'alimentation par voie intraveineuse. Ils ont surveillé personnellement tous leurs malades et ont suivi plusieurs d'entre eux grâce au contrôle de leur équilibre métabolique. Ils ont expliqué en détail les raisons d'être physiologiques qui président à l'emploi, aujourd'hui classique, du mélange du soluté glucosé hypertonique et d'hydrolysat de protéine. Les auteurs insistent sur les précautions minutieuses qu'il faut prendre pour éviter les complications et passent en revue le diagnostic et le traitement de ces complications, qui surviennent inévitablement quand on a affaire à des malades très vulnérables. Dans une section spéciale, on trouve les modifications qu'il faut faire subir à la formule de base pour l'adapter aux besoins des hépatiques, des cardiaques et des néphropathes. Ils consacrent beaucoup de temps à exposer les détails délicats qui concourent à la sécurité du mélange et le contrôle pharmaceutique des solutions nutritives. Cet article détaillé devrait permettre à n'importe quel médecin d'instaurer une suralimentation intraveineuse dans son hôpital, quelle que soit l'importance de ce dernier et indépendamment de son encombrement en malades.

MEDIASTINAL MALIGNANT LYMPHOMAS

A clinical analysis of 97 patients with mediastinal malignant lymphomas is reported. The ratio of female to male patients was 1.3:1, with an average age of 36.1 years for the 55 women and 37.2 years for the 42 men. Specifically, in mediastinal Hodgkin's disease, the female to male ratio was 2.4:1, while in patients with lymphoblastic lymphoma the reverse was true, with a ratio of 1:2. The presenting symptoms in order of frequency were: cough in 30 patients, chest pain in 27, fever in 13, dyspnea in 12, weight loss in 12, palpable nodes in 18, and easy fatigability in six patients. Twenty-six other patients were asymptomatic.

Roentgenograms of the chest were the single most important diagnostic method. Rouleaux formation was found in 38.2% of the peripheral blood smears. Angiograms, thoracic arteriograms, and lymphangiograms may be used in the differential diagnosis.

Staging, based on the Peters and Middlemiss method, placed 15 lesions in Stage I, 31 in Stage II (substage 1), and 51 in Stage II (substage 2). Hodgkin's disease composed 58.7% of the mediastinal lymphomas. In 35 patients, the structure of the diseased tissues was characteristic of nodular sclerosis and, in 19 patients, showed a diffuse mixed cellularity.

Thirty-five patients had exploratory thoracotomy with biopsy, 16 patients had thoracotomy with curative resection and 38 had supraclavicular node biopsy. The overall five-year survival rate for the entire group was 39.1%, while the 10-year survival rate was 17.1% and consisted only of Hodgkin's disease survivors. The survival rate for female patients was 49.1% and for men was 31.7%. Of the patients with lymphoblastic lymphomas, only two survived for two years. Surgical excision of the mediastinal lesion with subsequent radiation therapy seemed to yield the most striking results, as evidenced by the fact that 13 of the 16 patients in this group survived for five years. In contrast, among 80 patients who did not undergo operation, there were only 32 survivors. A more aggressive surgical attitude seems to be indicated especially in combination with radical radiotherapy.—Van Heerden JA, Harrison EG, Bernatz PE, et al: Mediastinal malignant lymphoma. *Chest* 57: 518, 1970

INVAGINATION FOR CONTROL OF REFLUX AFTER ESOPHAGOGASTRIC ANASTOMOSIS*

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REFLUX esophagitis and stricture frequently follow esophagogastrectomy. This operation, which resects the gastroesophageal sphincter and creates a hiatus hernia, removes the major antireflux mechanisms[1-3] and exposes the esophagus to free reflux of gastric contents. Belsey[4] reported that 27% of his patients developed esophageal stricture within six months of esophagogastrectomy. Because of this complication, many surgeons have attempted to construct a barrier to reflux, but their success is in doubt because these studies lack adequate follow-up in either experimental animals or humans.

Surgeons have attempted to control reflux: by running the esophageal remnant through a submucosal gastric tunnel,[5] by creating a lower esophageal flap valve,[6] by invagination of the esophagus into the stomach and covering it with gastric mucosa,[7] by wrap-around invagination of the esophagus into the stomach,[8] and by creating a new esophagogastric-sphincter zone with innervated diaphragmatic muscle.[9]

Clinically, there is some evidence that a 4- to 6-cm. invagination of the esophagus into the stomach decreases reflux and slightly lowers the incidence of postoperative strictures.[10] This clinical finding was investigated to determine experimentally the authenticity of an invagination anastomosis and to establish the length of anastomosis necessary to prevent reflux.

METHOD

Eighteen healthy 20-kg. dogs were studied preoperatively and postoperatively. Preoperative studies included three esophageal motility records, and a cine barium swallow followed by esophagoscopy and biopsy of the esophagus. Manometric studies were carried out using three Pe 240 polyethylene tubes with side openings and constant water infusion at 3.6 c.c./min./tube. Changes in the intraluminal pressure were measured by P23De Statham strain gauges and recorded by a Honeywell 1508 visicorder. The tubes were passed into the stomach of conscious trained dogs and continuous readings made during the period of 1-cm., staged, tube withdrawal.

In each dog the preoperative findings were considered to be within normal limits. Manometric studies in the normal dog demonstrated the high pressure zone (HPZ) at the gastroesophageal junction. The HPZ contained the point of respiratory reversal where inspiratory positive abdominal waves changed to inspiratory negative thoracic waves. The response of the HPZ to deglutition was one of relaxation followed by contraction. In the body of the esophagus, peristaltic waves followed each deglutition and no significant disorder of peristaltic waves was found in these dogs.

Following complete preoperative study, an esophagogastrectomy was performed in each dog. A left thoracotomy was made, excising the eighth rib. The stomach was mobilized through the esophageal hiatus. A 3-cm. cuff of esophagus and a 2-cm. cuff of stomach were excised and a vagotomy and pyloromyotomy performed.

Three types of esophagogastric anastomosis were constructed in these dogs (Fig. 1). In Group I, six dogs had an end-to-end esophagogastric anastomosis. In Group II, five dogs had an end-to-end esophagogastric anastomosis; then the esophagus was invaginated into the stomach for a distance of 2 to 4 cm. In Group III, seven dogs had the same operation but the invaginations were 4 to 5½ cm. in length.

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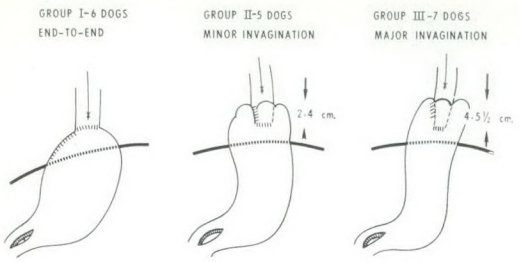

Fig. 1.—Esophagogastrectomy with three types of anastomoses: (1) end-to-end, (2) minor invagination, (3) major invagination. All dogs had a vagotomy and pyloroplasty as part of the operation.

The dogs were allowed a minimum of 10 days to recover from the operation before postoperative studies were done. The investigations done before operation were now repeated in each dog.

At least three postoperative motility studies were done, with additional studies in "long-term" dogs. Each dog had one or more cine barium swallow studies, and reflux was tested by placing the dog in the Trendelenburg position and applying abdominal compression. Esophagoscopy and biopsy were done immediately before sacrifice and autopsy.

Postoperative Results

Esophageal Motility Tests

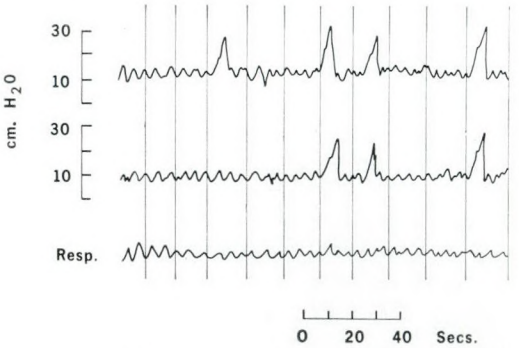

Fig. 2.—End-to-end esophagogastric anastomosis. The upper two traces are from separate esophageal tubes 5 cm. apart, the upper tube being more proximal. The lower tracing is a recording of respiration. Vertical lines mark each 1-cm. move as the tubes are withdrawn proximally in the esophagus. The esophagogastric anastomosis is marked by the presence of peristaltic waves. There is no effective pressure barrier between stomach and esophagus and no fall in pressure at the point of anastomosis.

TABLE I.—Average Gastroesophageal Pressure Gradient

Dogs	*Resting pressure gradient (cm. H_2O)*	*Abdominal compression pressure gradient (cm. H_2O)*
Before operation	12	17
Group I: end-to-end anastomosis	1.6	0.5
Group II: 2- to 4-cm. invagination	8	9
Group III: 4- to 5½-cm. invagination	10	15

Group I.—In the dogs with end-to-end anastomoses (Fig. 2) there was no effective pressure barrier between the stomach and the esophagus. There was a gradual fall in pressure as the tubes were pulled up the esophagus and the lower and mid-esophageal pressures were elevated. When abdominal compression was applied, there was no elevation of esophageal pressure (Table I). In this table, results of preoperative esophageal motility studies show that a gastroesophageal pressure gradient has been maintained. Dogs with end-to-end esophagogastrectomy do not have this gradient. The dogs with 4- to 5½-cm. invagination anastomosis could maintain a

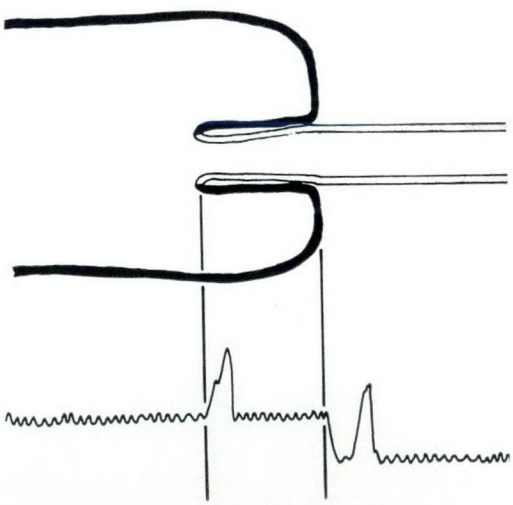

Fig. 3.—Diagram of esophagogastric anastomosis and invagination to show the relationship of the esophageal pressure changes to the invagination. In Fig. 4 an actual pressure pattern is illustrated in dogs with 5½ cm. of invagination. The lower esophagus is maintained at gastric pressure by the invaginating stomach. The fall in pressure to esophageal levels occurs at the upper margin of the invagination.

normal pressure gradient between stomach and esophagus, even when abdominal pressure was applied.

Group II.—In these dogs with invaginations of less than 4 cm., the results were variable. In some, there was evidence of a small pressure drop at the upper end of the invagination but this was less than in the 4- to 5½-cm. invagination dogs (Fig. 3). Elevation of abdominal pressure caused a rise in esophageal pressure indicating that there was no effective barrier to reflux.

Group III.—Seven dogs in this group all showed a well-defined pressure drop at the upper end of the invagination (Fig. 4).

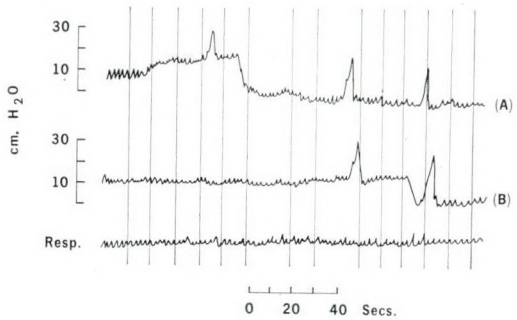

Fig. 4.—Invagination esophagogastrectomy pressure tracing. The pressure traces are the same as in Fig. 2. In this case, the esophagogastric anastomosis is marked by the presence of esophageal peristaltic waves. The invaginated distal esophagus is maintained at gastric pressure by the invaginating stomach and the pressure fall takes place at the upper end of the invagination (Fig. 3).

This pressure barrier, unlike those in the studies in Groups I and II, was completely maintained during abdominal compression and, in addition, there was no rise in esophageal pressure.

The esophagogastric anastomosis was recognized in all dogs by the presence of esophageal peristaltic waves. In the invaginated esophagus, the short segment of invaginated esophagus was maintained at gastric pressure, and the pressure fall occurred at the upper end of the invagination (Fig. 3).

Radiographic Studies

Group I.—These six dogs with end-to-end anastomosis had free reflux up to the pharyngoesophageal junction (3+). These

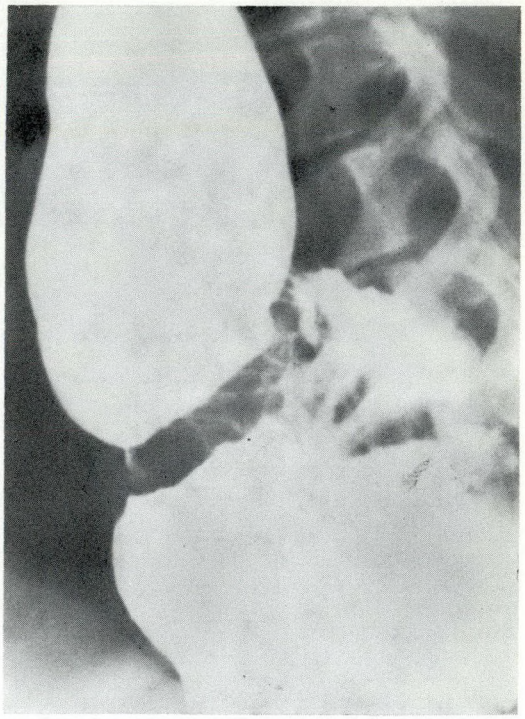

Fig. 5.—End-to-end esophagogastric anastomosis with free reflux to the pharyngoesophageal junction. Free reflux occurred with or without abdominal compression.

dogs refluxed while lying prone without abdominal pressure or Trendelenburg positioning (Fig. 5).

Group II.—All of these five dogs had reflux to a varying degree. One had only a trace (1+). The remaining four had moderate (2+) to severe (3+) reflux (Fig. 6).

Group III.—Of the seven dogs with invaginations of 4 to 5½ cm., one with a 4-cm. invagination had 1+ reflux. The remaining six had no reflux despite the use of the Trendelenburg position and abdominal compression (Fig. 7).

Pathology

In all dogs, esophageal biopsy taken before operation showed a normal macroscopic appearance. At the end of the study, the dogs were killed and their esophagi studied grossly and microscopically.

Group I.—The dogs with end-to-end anastomoses were killed at one month (two dogs), two months (two dogs), and three months (two dogs). One dog killed at two

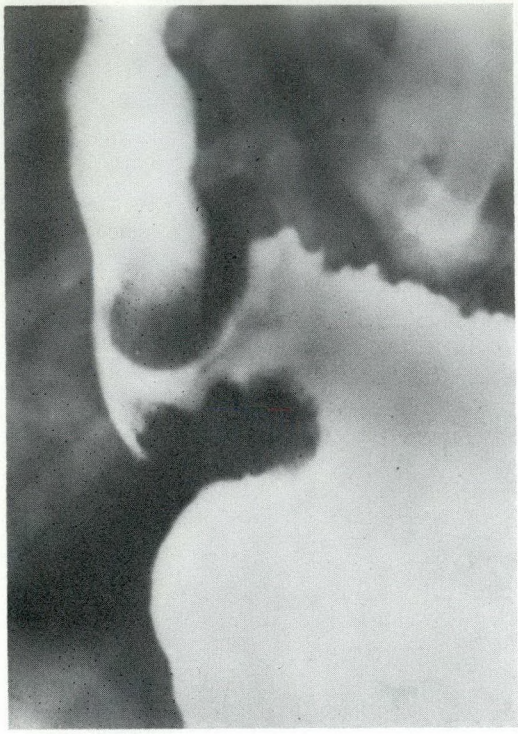

Fig. 6.—Small invagination esophagogastric anastomosis with moderate reflux. The short invaginated segment can be seen surrounded by gastric fundus. Free reflux was present with or without abdominal compression.

months and one at three months showed only a trace of esophagitis. Both of these dogs had free reflux and no effective barrier on motility studies. The remaining four had severe esophagitis with active and healed ulceration extending to a maximum of 10 cm. above the esophagogastric anastomosis.

Group II.—In this group, four dogs were killed at one month. Two had severe esophagitis comparable to the Group I dogs; the other two dogs had localized esophagitis with small healed ulcers. One dog was killed at three months and had slight esophagitis with localized inflammation and a small ulcer.

Group III.—In this group, four dogs were killed at one month and three at two months. One dog killed at one month had a small ulcer at the esophagogastric anastomosis. This dog had a trace of reflux on cine barium swallow. The remaining three had no evidence of esophagitis grossly or microscopically.

Discussion

This study showed that reflux was prevented by a 4- to 5½-cm. invagination of

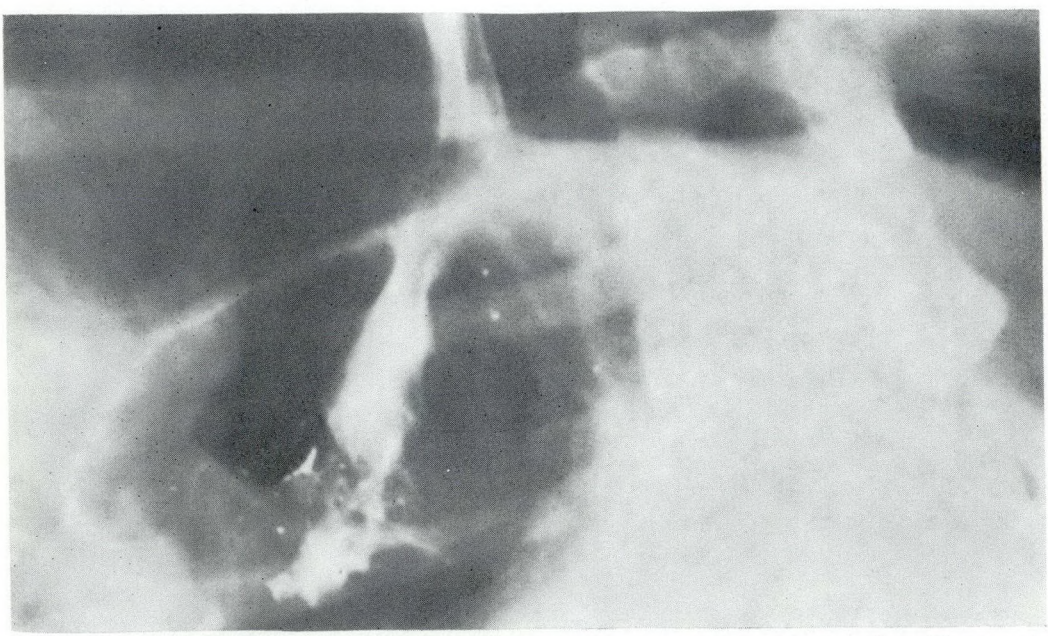

Fig. 7.—Large (5½-cm.) invagination esophagogastric anastomosis with no reflux. The invaginated esophagus can be seen surrounded by air-filled stomach. Application of abdominal pressure emptied the barium from the invaginated esophagus, illustrating the flap-valve method of maintaining closure of this segment.

esophagus into the stomach. The effectiveness of this antireflux mechanism was studied by radiology, manometry, esophagoscopy and by the autopsy pathology. Radiologically, free reflux was seen in all dogs with simple end-to-end anastomoses, and with anastomoses less than 4 cm. in length. Many of these dogs developed esophagitis. Dogs with invaginations of more than 4 cm. showed no evidence of reflux.

The mechanism that prevents reflux can be identified by studying the esophageal motility records in the dogs with a 4- to 5½-cm. invagination. The invaginated esophagus was maintained at gastric pressure by transmission of gastric pressure within the invagination. At the upper end of the invagination, the pressure fell to normal esophageal levels, indicating that an effective pressure barrier existed which prevented transmission of gastric pressure to the remaining esophagus. In this way, the stomach is used as a means of transmitting gastric pressure to the invaginated intrathoracic esophagus and maintaining closure of the invaginated esophageal segment. By closing this segment, an effective flap-valve antireflux mechanism is created. We obtained further confirmation of the authenticity of invagination by studying 11 patients with established invagination esophagogastrectomies.[11] In these subjects, we found no motor, pH or radiologic evidence of reflux and, in all, gastric pressure fell at the proximal margin of the invagination.

In three patients with high esophagogastric anastomoses, slight reflux could be demonstrated. In these patients because of the considerable length of stomach within the thoracic cavity, effective gastric pressure was not maintained up to the point of anastomosis. Because of the lowered intragastric pressure, a less effective flap-valve mechanism was constructed. These data are made more difficult to interpret because, with high invagination anastomoses, ample stomach is not always available for full invagination. Nevertheless, this observation suggests that the most effective anastomosis is created in the lower two-thirds of the chest because, in this position, gastric pressure is well maintained and the flap-valve mechanism is most effective.

Conclusions

After esophagogastrectomy, an invagination esophagogastric anastomosis produces a "competent sphincter" at the gastroesophageal junction. Intra-abdominal positive pressure acting upon the junction maintains an effective pressure barrier. In this study, we demonstrated that, to control reflux in dogs, at least 4 cm. of esophagus has to be invaginated.

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Résumé

L'œsophago-gastrostomie réalisée par anastomose termino-terminale s'accompagne souvent de régurgitation, d'œsophagite et de rétrécissement. Plusieurs chercheurs avaient déjà signalé que l'invagination de l'œsophage à l'intérieur de l'estomac est une technique opératoire qui constitue en soi un mécanisme efficace contre la régurgitation. Le présent article a pour objet d'étudier le bien-fondé de cette technique et de préciser sa fonction au point de vue mécanique.

Nous avons observé trois groupes de chiens, avant et après œsophago-gastrostomie et avons notamment mesuré la motilité de l'œsophage, examiné par cinéradiographie la progression du baryum durant la déglutition. Après avoir sacrifié les animaux, nous avons procédé à la nécropsie

et à l'examen pathologique. Dans le groupe I, la technique utilisée était une anastomose termino-terminale. Ces animaux présentaient des régurgitations constantes et la plupart souffraient d'œsophagite. Dans le groupe II, la technique avait consisté en une invagination de 2 à 4 cm de profondeur. Les résultats ont été variables, mais tous les animaux présentaient des régurgitations épisodiques. Dans le groupe III, on pratiqua une invagination avec anastomose. Chez aucun des animaux du groupe, on ne notait ni régurgitation, ni œsophagite.

Au moyen d'un manomètre intra-œsophagien, nous avons pu démontrer que l'œsophage invaginé agissait à la manière d'une valve à clapet maintenue fermée par la pression gastrique régnant dans la portion d'estomac entourant l'anastomose. Nous avons conclu que l'invagination de l'œsophage au sein de l'estomac empêche réellement la régurgitation.

INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation has been defined as acute transient coagulation occurring in the blood flowing throughout the microcirculation. The authors determined the coagulation abnormalities associated with the shock state in humans and correlated the findings with the pathologic studies of patients in a shock state who died. Two hundred and ninety-four patients in a state of shock were studied. A patient was considered to be in shock when the arterial pressure was below 90 mm. Hg with a central venous pressure variable depending on the specific type of shock, with or without low cardiac output, with acid-base imbalance, and with impaired renal function.

The frequent association of shock in disseminated intravascular coagulation has been demonstrated in the experimental animal, and considered as a cause of irreversibility. The authors cite a number of studies that they believe clearly support the concept that a shock state in humans is not responsible for histologically detectable, widespread disseminated intravascular thrombosis, as occurs in experimental animals. There were 146 deaths in the reported series with 78 autopsies. There was little evidence of intravascular fibrin deposition in the liver, lungs, or kidneys. The most consistent change noted was found in the liver (dilatation and congestion of the sinusoids and hepatic veins).

The authors found, in those who died, a significant depletion of clotting factors V, VII, IX, X and XI. The authors explained the significant coagulation abnormalities by two possible hypotheses. Disseminated intravascular coagulation does exist because normally fibrin is constantly being formed intravascularly, and degraded by the fibrinolytic system. The compensatory mechanisms of fibrinolysis and clearance of fibrin deposition occur and evidence for disseminated intravascular coagulation will be lacking after death, although significant coagulation abnormalities were present *in vivo*. The second possibility is that the coagulation and fibrinolytic changes observed in shock are secondary to the parenchymatous changes seen in the hypoxic liver. Since the liver is the site of production of almost all clotting factors, its involvement can explain the coagulation abnormalities observed in the shock state. Hepatic changes do occur in shock and are thought to be related to the duration of the state of shock; that is, if it exists for more than 24 hours, hepatic necrosis is almost constant. If it lasts less than 10 hours, it is unusual. The decrease in blood flow through the portal vein, as well as the hepatic artery during a state of shock, will reduce the oxygen tension in the centrizonal cells, causing greater anoxic changes than in the peripheral cells and lead to necrosis. The activation of the fibrinolytic system occurs through tissue hypoxia and increased catecholamines, a decrease in fibrinolytic inhibitor, and failure of hepatic clearance of plasminogen activator. It accounts for the decrease in fibrinogen and other clotting factors.

In summary, the authors conclude that significant alterations in the coagulation and fibrinolytic systems were demonstrated in 294 patients in a state of shock. These changes could be interpreted as resulting from disseminated intravascular coagulation. However, in 52 bodies examined carefully at autopsy, there was no evidence of fibrin deposition. The most consistent pathologic changes were seen in the liver and ranged from sinusoidal dilatation to extensive hepatic necrosis. It was concluded by the authors that disseminated intravascular coagulation may not play a major role in the irreversible stages of shock in humans.—Attar S, Hanashiro P, Mansberger A, et al: Intravascular coagulation; reality or myth? *Surgery* 68: 27, 1970

RENAL ANGIOMYOLIPOMA: DIAGNOSIS AND SURGICAL MANAGEMENT*

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In this paper we propose to present diagnostic criteria for renal angiomyolipoma, review current surgical management, and describe the authors' concept of surgical management of this lesion, with particular reference to the solitary lesion in a patient in the hypernephroma age group who has minimal or no clinical findings of the tuberous sclerosis complex. In addition, a typical case will be reported.

Pathologic Background

In 1862 von Recklinghausen first described patchy sclerosis of the cerebral cortex in a patient who also had multiple myomas of the heart. Bourneville later applied the name "tuberous sclerosis" to the cerebral changes. The term "epiloia" was introduced by Sherlock, in 1911, to indicate the commonly encountered triad of adenoma sebaceum, epilepsy and mental deficiency. In 1942 Moolten[1] suggested the name "tuberous sclerosis complex", because the term "tuberous sclerosis" applied only to one feature in this disorder of multiple abnormalities.

In the fully developed tuberous sclerosis complex, the individual may have numerous and diverse hamartomas in the brain, kidneys, bones, skin, heart and lungs. The cerebral lesions consist of collections of dense glial tissue in patchy distribution. In the retina these are known as phacomas. Of the skin lesions the most common, adenoma sebaceum, consists of groups of nodules which occur most often near the nose. Histologically these show increased dermal collagen and hair follicles, and a proliferation of sebaceous glands. Less common skin lesions are thickened patches near the sacrum, shagreen patches, and hyperpigmented *café-au-lait* spots. Ungual fibromas also occur. Other lesions sometimes found in this complex are cardiac rhabdomyomas, hepatic hamartomas and cystic pulmonary lesions. Bone changes include patchy localized densities in the skull, vertebral column and pelvis which may simulate osteoblastic metastases.

The renal lesion, which occurs in 50% to 80% of tuberous sclerosis patients, has been named "renal angiomyolipoma". Approximately 50% of such lesions reported to date have been found in patients who do not have other evidence of the tuberous sclerosis complex.

The renal lesions are composed of unencapsulated adipose tissue, smooth muscle, and blood vessels, in varying proportions. Several authors[2-4] have reported that in the absence of a demonstrable tuberous sclerosis complex, renal angiomyolipomas usually present as a single lesion in only one kidney. Such isolated lesions are more common in females.[5, 6] Patients afflicted with the tuberous sclerosis complex generally have multiple angiomyolipomas in both kidneys. These patients may be of either sex but are younger than those with only an isolated kidney lesion.

The leading cause of death attributable to the renal angiomyolipoma itself is exsanguinating hemorrhage. Although it is often stated that renal angiomyolipomas frequently lead to renal failure, only one such report was found in the literature.[7]

The incidence of tuberous sclerosis has been variously reported as one in 250 in psychiatric populations to one in 300,000 in the general population. Although it was widely held that 75% of tuberous sclerosis patients die before reaching 25 years of age, several authors have observed otherwise.[8] Patients with tuberous sclerosis complex most commonly die of cerebral hemorrhage or in status epilepticus.

The high mortality rate would apply only to those patients who have a fully developed clinical picture of tuberous sclero-

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sis complex. It has now become apparent that formes frustes of this disease exist which include patients with normal intelligence. In analyzing pedigrees of tuberous sclerosis, Marshall, Saul and Sachs[9] concluded it is due to a rare autosomal dominant gene. Since the trait is known to skip a generation, they believe that the expression of the basic gene is affected by an independent pair of modifying genes. Thus mild forms of the complex can occur where only a single somatic system is affected or severe cases in which two or more systems are affected. Also, normal individuals can carry the gene.

Histogenesis and Pathology

Although we know little about the etiology of renal angiomyolipomas, these tumours appear to be benign hamartomas on the basis of histologic appearance and clinical behaviour.

Inglis[10] in 1954 proposed that the renal tumours, like the cerebral nodules in tuberous sclerosis, were of neural origin. In 1960, after further study, he recognized that his original interpretation was wrong.[11] Inglis now regards these tumours as a distinct type, whether or not they are single or multiple or associated with tuberous sclerosis. His reasons are: (1) In all of these lesions the arteries have no internal elastic lamina in the walls. (2) The smooth-muscle-like cells of these tumours resemble myoid cells of the cutaneous glomus. He believes that a common histogenetic factor underlies glomus tumour, angioleiomyoma and the renal tumour of the tuberous sclerosis complex. (3) He does not believe that the smooth-muscle elements in angiomyolipoma are ordinary smooth muscle, but has not decided whether the smooth muscle in the walls of the blood vessels contributes to the formation of these tumours.

Most of the controversy regarding the etiology of renal angiomyolipoma centres around the smooth-muscle cells. Allen and Risk[12] noted that the smooth muscle is usually the wildest element of the tumour, sometimes showing cellular pleomorphism and mitoses characteristic of malignancy. Lucké and Schlumberger[13] concur but point out that any of the elements may show pleomorphism.

Moolten[1] considers the renal lesion to be a hamartoma. In his view the three tissues that comprise the lesion arise from nests of embryonal cells which remain in a state of permanent embryonicity because of a failure of induction. According to Moolten only three patients with renal angiomyolipomas and tuberous sclerosis have had small metastatic deposits in other organs that were unmistakably malignant.

When patients with supposedly malignant variants of this renal tumour have been irradiated after nephrectomy, they did well and survived with no evidence of local recurrence or distant metastases.[6, 12] Allen and Risk[12] found no report of deaths from metastatic angiomyolipoma in the literature. Perou and Gray[6] believe that even though isolated angiomyolipomas may contain immature cells and be invasive, they are not true malignant tumours. Because of its benign clinical course, most authors have been reluctant to call angiomyolipoma malignant regardless of its gross or microscopic appearance.

Case Report

A 13-year-old white girl with tuberous sclerosis was readmitted to the University of Alberta Hospital, Edmonton, on December 24, 1967. In 1964 she had been admitted because of reddish maculopapular lesions covering both cheeks in a butterfly pattern. These had been diagnosed clinically as adenoma sebaceum (Fig. 1). At that time and on three subsequent occasions, the skin lesions had been abraded for cosmetic reasons. The other stigmas of tuberous sclerosis which she exhibited included: (1) phacomas of the retinas, (2) small fibroadenoma of the scalp, (3) shagreen patch on the back and (4) a history of convulsive episodes beginning at 6 months of age and disappearing at the age of 2 years. She had failed to pass Grade 3 in school and had subsequently progressed with low grades. Her mother said she had developed normally, sat up at 5 months of age and walked at 11 months. There was no family history of convulsions, facial acne or mental retardation.

In April 1966 an effort was made to determine the presence or absence of other lesions of the tuberous sclerosis complex. On intravenous pyelograms the calyces of the left kid-

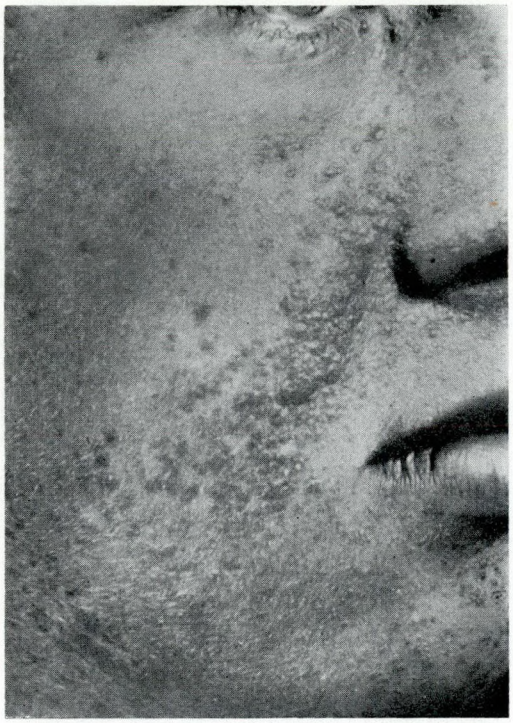

Fig. 1.—Appearance of adenoma sebaceum before dermabrasion.

ney were distended, blunted and markedly distorted, giving the impression that they were deformed by a tumour. The upper-pole calyces of the right kidney were widened, suggesting possible early distortion (Fig. 2).

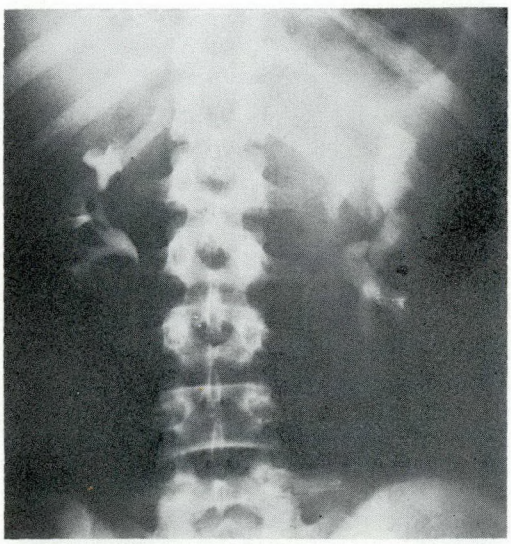

Fig. 2.—Intravenous pyelogram showing tumour deformity of the left kidney calyces and possible early distortion of the upper-pole calyces and infundibulum of the right kidney.

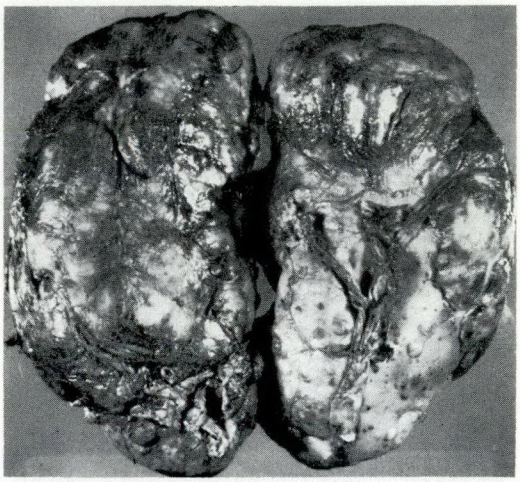

Fig. 3.—Gross specimen of the left kidney showing distortion of reniform configuration by nodular masses.

In October 1967 while playing she had a sharp pain in her left side that was not associated with external trauma. Gross hematuria occurred a few hours later and she was readmitted to the hospital for observation. Within the next five days the hematuria subsided.

On December 24, 1967 she again experienced spontaneous left flank pain followed by profuse gross hematuria and, on admission to the hospital, was treated for hypovolemic shock. Profuse gross hematuria persisted and she was taken to the operating room for an emergency left nephrectomy. At operation the left kidney was found to be 1½ times the normal size and the perirenal fascia was ad-

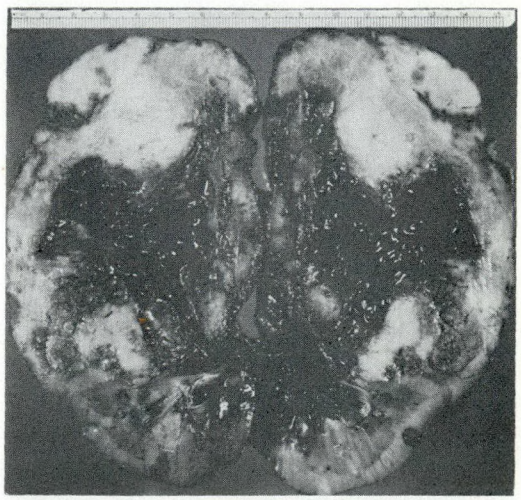

Fig. 4.—Gross specimen of the bivalved left kidney showing replacement of normal parenchyma and fresh clot in the renal pelvis.

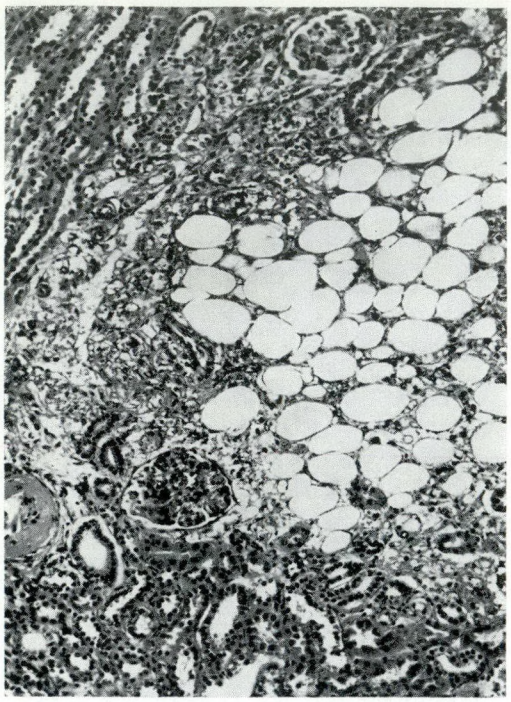

Fig. 5.—High-power photomicrograph demonstrating a typical area of parenchymal replacement by non-encapsulated fat (H & E, original magnification X 125).

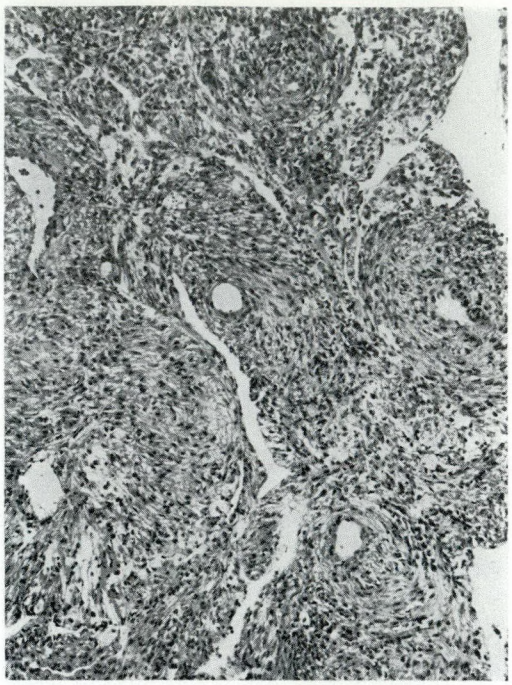

Fig. 6.—High-power photomicrograph demonstrating many atypical arteries with absent internal elastic laminas and continuity of the arterial walls with the bundles of smooth-muscle-like cells in the interstitium (H & E, original magnification X 125).

herent and edematous. The cortex of the kidney contained scattered yellowish nodules, and the upper pole contained an irregular mass the size of an orange. The patient's recovery was uneventful.

The kidney weighed 385 g. and measured 14 x 7 cm. The renal parenchyma was replaced by yellow, somewhat trabeculated, tumour tissue. Only a small segment of the lower pole was recognizable as kidney tissue. The cortical surface was studded with yellow nodules measuring 0.2 to 0.5 cm. in diameter. The renal pelvis and calyces were filled with blood (Figs. 3 and 4).

Histologically the tumour was typical of angiomyolipoma. There were areas of non-encapsulated fat, smooth-muscle cells and atypical blood vessels with no inner elastic lamina. There was no malignant transformation (Figs. 5 and 6).

Follow-up intravenous pyelogram 34 months later revealed no progression of the suspected right upper-pole lesion.

Differential Diagnosis of Renal Angiomyolipoma

Although renal tumours generally produce few symptoms until late in the course of the tuberous sclerosis complex, sharp pain in the kidney area and syncope indicating internal hemorrhage should focus attention on a possible angiomyolipoma.[6] An intravenous pyelogram will reveal a space-occupying lesion which distorts the calyces and even the renal pelvis. Areas of increased radiolucency within the kidneys are often seen during urographic studies. These are attributed to hemorrhage, infarction or collections of fat within a tumour. This finding can also suggest multiple cystic areas, and thus polycystic disease must be considered.

A tumour deformity on intravenous pyelogram in a patient with cutaneous lesions and radiographic evidence of tuberous sclerosis in bones or brain should suggest renal angiomyolipoma regardless of the age of the patient. If the renal lesions are bilateral, the diagnosis even more strongly favours angiomyolipoma.

The surgeon's diagnostic abilities and criteria are most severely tested in the patient with some or no clinical findings of

the tuberous sclerosis complex and a unilateral renal lesion seen on intravenous urography. In this situation he may be helped by the arteriographic findings reported by Viamonte *et al.*[14] in a typical case of renal angiomyolipoma in a patient with tuberous sclerosis. On performing selective renal arteriography, they found changes which they interpreted as characteristic of angiomyolipoma and by which they could differentiate this lesion from hypernephroma or polycystic disease. In the arterial phase there was hypervascularity and abnormal distribution of vessels. There was loss of normal tapering and also tortuosity of the arteries as in hypernephroma. However, small regular outpouchings from the interlobar and interlobular arteries were seen. These resembled "berry" aneurysms and the appearance of the artery at its termination suggested a cluster of grapes. Puddling of contrast material was also observed as in hypernephroma. The venous phase developed normally in contrast to the early appearance often associated with hypernephroma. No arteriovenous fistulas were seen. Polycystic renal disease could be ruled out easily because it has a relatively avascular angiographic pattern. These findings suggested the true diagnosis to Viamonte *et al.* before other stigmas were sought.

Surgical Management of Renal Angiomyolipoma

Surgical exploration is often performed in order to establish the diagnosis of renal angiomyolipoma in suspected cases. According to Van Heerden *et al.*,[15] all such patients should be explored, except those with bilateral multiple lesions. They believe there is no indication for complete or partial nephrectomy when the lesions are bilateral. If the lesion is unilateral and partial nephrectomy is possible, it should be performed.

McQueeney, Dahlen and Gebhart[16] argue that the needless sacrifice of a kidney for a benign tumour may often be avoided by biopsy and examination of a frozen section. They acknowledge the risk of disseminating the tumour if it is malignant by taking the biopsy. They believe that once the diagnosis has been made, conservative local excision is adequate treatment. Straffon[17] explores all patients with suspected renal angiomyolipoma to rule out a necrotic hypernephroma.

Allen and Risk[12] warn that there is no plane of cleavage between the angiomyolipoma and normal kidney. Morphologically the large masses of fat in these tumours are not encapsulated. There is a potential risk of brisk hemorrhage on attempting partial nephrectomy. Furthermore these lesions possess a growth potential and may recur if incompletely excised.

Our concept of the surgical management of renal angiomyolipomas is based on the following considerations: This lesion, whether it is associated with tuberous sclerosis or not, is a hamartoma and benign in behaviour. The main cause of death attributable to renal angiomyolipoma is exsanguinating hemorrhage. Many angiomyolipomas are small and are totally asymptomatic. Of patients afflicted with the tuberous sclerosis complex, renal angiomyolipomas generally occur in both kidneys. Patients with mild forms of the tuberous sclerosis complex live to an older age and therefore renal angiomyolipomas may appear in those in the hypernephroma age group. There may be specific arteriographic signs of renal angiomyolipoma. If substantiated, these will enable a more definitive preoperative diagnosis. There is a poor plane of cleavage between normal kidney and the angiomyolipoma. Therefore in attempted partial nephrectomy there is the risk of possible hemorrhage which may necessitate total nephrectomy. Renal angiomyolipomas may recur if incompletely excised.

Our current approach to the diagnosis and surgical management of renal angiomyolipomas is as follows: we do a personal and family history, and a careful physical examination seeking stigmas of the tuberous sclerosis complex. Each patient has an intravenous pyelogram, nephrotomogram and renal arteriogram, and chest, skull and skeletal radiographs.

The patient who has the stigmas of both tuberous sclerosis and bilateral renal lesions

should have no operation, except that necessary to control life-threatening hemorrhage. If there are large bilateral lesions and massive hemorrhage from one kidney, we would attempt partial nephrectomy after first gaining access to the renal artery so that it may be quickly clamped should uncontrollable hemorrhage persist. In patients who have the tuberous sclerosis complex and a unilateral angiomyolipoma, and are less than 40 years of age, nephrectomy is performed only for uncontrollable hemorrhage. If a patient with these lesions is not bleeding but is in the hypernephroma age group, nephrectomy is performed. Although most of these lesions are likely to be angiomyolipomas, present diagnostic procedures do not provide a definitive preoperative diagnosis and we believe that biopsy of renal tumours cannot be justified. Furthermore, the risk to life is greater from an overlooked adenocarcinoma than from the subsequent development of an angiomyolipoma in the other kidney.

Patients who have a unilateral tumour deformity on urographic examination but have none of the stigmas of tuberous sclerosis should have a nephrectomy. Rarely, histologic examination will show that the lesion is an angiomyolipoma. If so, the surgeon need have no concern over the subsequent development of a similar lesion in the remaining kidney because bilateral angiomyolipomas do not develop except in patients with the tuberous sclerosis complex.

Summary

Renal angiomyolipoma may occur in the absence of tuberous sclerosis. Whether or not it is associated with the tuberous sclerosis complex, it behaves as a benign lesion. Because the tuberous sclerosis complex is incompletely expressed in some patients, these individuals live to an older age than was earlier realized. Because the angiomyolipoma appears as a tumour-deformity on intravenous pyelography, it must be differentiated from hypernephroma, particularly in those patients 40 years or older, and because unilateral renal angiomyolipomas usually occur in the absence of the tuberous sclerosis complex. Recently certain arteriographic signs have been reported as specific for renal angiomyolipoma. If substantiated, these may enable a more definite preoperative diagnosis.

The surgical management proposed is more conservative than has heretofore been advocated. Patients with stigmas of tuberous sclerosis and who have the renal lesion should be treated by nephrectomy only to control life-threatening hemorrhage. Partial nephrectomy is not recommended. Those patients with unilateral angiomyolipomas who are in the hypernephroma age group should have a nephrectomy regardless of the presence or absence of the tuberous sclerosis complex.

In addition, the literature on the subject is briefly reviewed and a typical case is reported.

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Résumé

L'angiomyolipome rénal, qui est une dysembryoplasie bénigne, peut survenir en l'absence de sclérose tubéreuse. Les malades qui souffrent du complexe de sclérose tubéreuse ont généralement des angiomyolipomes dans les deux reins, tandis que ceux qui ne sont pas affectés de sclérose tubéreuse, ont couramment des tumeurs unilatérales. Les malades qui présentent des formes bénignes de ce complexe vivent jusqu'à un âge avancé et, par conséquent, les masses rénales unilatérales doivent être différenciées d'un hypernéphrome. On a signalé avoir trouvé des signes artériographiques spécifiques d'angiomyolipome de sorts que, si on les découvre, on pourra poser un diagnostic plus précis. Les auteurs exposent un mode opératoire plus conservateur des angiomyolipomes rénaux. La cause principale du décès attribuable à l'angiomyolipome est l'exsanguination par hémorragie. Chez les malades souffrant du complexe de sclérose tubéreuse, la néphrectomie n'est recommandable que dans ce type de situation tragique. Les malades qui n'ont de tumeurs rénales que d'un côté et qui ont plus de 40 ans devraient être soumis à la néphrectomie, indépendamment de la présence ou de l'absence du complexe de sclérose tubéreuse. Les auteurs présentent un cas typique et passent brièvement en revue la littérature pertinente.

SPLENIC ABSCESS

The most common cause of splenic abscess is a focus of infection elsewhere in the body. A splenic abscess almost always occurs in an abnormal spleen. Although the mortality rate is high, the combination of well-timed surgical procedures and antibiotic therapy can be curative.

The study presents three patient reports representing three varieties of splenic abscess—arterial spread, trauma, and intra-abdominal suppuration. The first patient showed a background of cerebral embolism suggesting bacterial endocarditis. A history of pain in the left lower portion of the chest and in the upper portion of the abdomen suggested the possibility of splenic abscess. The roentgenograms showed the hemidiaphragm to be elevated. Needle aspiration yielded purulent material. The spleen was removed and contained splenic abscesses. The patient apparently had a splenic infarct on the basis of her sickle cell disease or bacterial endocarditis, and then the infarct subsequently became infected.

The second patient was a 16-year-old boy who had trauma to his left side, and subsequently had a pustule develop on his elbow. His course suggested hematogenous spread of bacteria from the pustule to an intrascapular splenic hematoma resulting from the previous trauma. The preoperative diagnosis of splenic abscess was made, the spleen was removed, and the abscess drained. Subsequently, the patient's course was complicated by apparent subphrenic abscess, bleeding in the upper portion of the gastrointestinal tract, and finally cholecystitis which necessitated cholecystostomy.

The third patient, a 58-year-old man, had a laparotomy in 1962 because of peritonitis secondary to perforated diverticulum. At that time, a colostomy was done. Subsequently he had numerous episodes of fever. In 1967 he had right upper quadrant pain and he had a cholecystectomy. Postoperatively, he did poorly and liver and spleen scans disclosed a large defect in the spleen; the diagnosis of splenic abscess was made. A splenectomy was performed and the wound drained. Confluent abscesses were found in the spleen. Antibiotic therapy in this patient was chloramphenicol 15 g. daily for seven days postoperatively and erythromycin 2 g. daily for three months. The outstanding characteristic of the third patient was the probable presence of an infected spleen for five years after perforation of the colonic diverticulum.

The high mortality rate associated with splenic abscess can be lowered by increased awareness, use of all diagnostic means, and prompt operation with appropriate antibiotic therapy. Laboratory data are not much help in diagnosis; however, the clinical course, roentgenograms showing elevated hemidiaphragm, and the use of splenic scanning were helpful.— Pickleman JR, Paloyan E, Block GE: Surgical significance of splenic abscess. *Surgery* 68: 287, 1970

OSTEOCHONDRITIS DISSECANS AND ANOMALOUS CENTRES OF OSSIFICATION: A REVIEW OF 80 LESIONS IN 61 PATIENTS

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THIS paper presents a clinical review of osteochondritis dissecans, a condition in which an osteochondral fragment gradually separates from an articular surface. This study, which was limited to the knee—the most common site of this lesion, is based on 80 joints in 61 patients. We propose that the osteochondritis dissecans in many of these patients developed on the basis of a pre-existing anomalous centre of ossification. We have not demonstrated the anomalous centre in any of these patients by radiographs but will present evidence of this hypothesis below. These patients do not seek medical advice until they develop symptoms; by that time, in our view, the centre has already separated. In this group, 30 patients were treated conservatively and 11 by surgical excision of the fragment. The fragment was extracted in 14 patients and pegged *in situ* in another eight cases.

ETIOLOGY AND PATHOGENESIS

Many explanations have been offered for osteochondritis dissecans of the knee; most of them fall into two categories: those based on ischemia and those on trauma. According to Fairbank,[1] osteochondritis dissecans results from the acute impingement of the tibial spine on the medial femoral condyle. Although many have supported this concept, and radiologists often report a "prominent" tibial spine, arthrotomy has provided little support for this theory. Moreover, the prominent spine does not explain osteochondritis dissecans in other joints and the occasional finding of more than one lesion in a single joint. The ischemic hypothesis assumes that the lesion follows infarction of the subchondral bone after end-artery occlusion. This occlusion has been attributed to fat emboli,[2] tubercle bacilli,[3] and erythrocyte aggregates.[4] This hypothesis does not explain the constant site of the lesions in contrast to the random distribution that characterized embolization.

We propose that the theories of ischemia and trauma are not necessarily mutually exclusive; both might operate when the lesion develops on the basis of an anomalous centre of ossification. These centres are common in the knee especially in the medial femoral condylar articular surface. In studying this condition, Ribbing[5] radiographed 291 children; Smillie[6] also described this condition in his text. Both authors concluded that there is a definite relationship between anomalies of ossification and trauma, and the subsequent development of osteochondritis dissecans. These anomalous centres of ossification appear to heal spontaneously, usually by the time the distal femoral epiphysis has closed. The condition "juvenile osteochondritis dissecans" probably represents asymptomatic anomalous centres that often heal spontaneously. The blood supply to these centres, which is via the bony nucleus of the distal femoral epiphysis, is presumably tenuous and susceptible to shearing forces.

Fig. 1 shows the forces that act at the articular surface of the knee. As the knee passes from flexion to extension, the femur rotates internally on the tibia—the "screw-home" effect. This rotation, which is associated with twisting of the anterior cruciate ligament around the posterior cruciate ligament and relative shortening of these structures, not only apposes the articular surfaces at the end of extension but produces a twisting force which is dissipated horizontally at the articular surface. We propose that this "torsional impaction",[7] a phenomenon of normal knees, twists the anomalous centre, and, by creating a horizontal plane of cleavage, ruptures its fragile nutrient vessels as they pass from the bony nucleus of the femoral epiphysis. Avascular necrosis of the centre follows. Repetition of torsional impaction with

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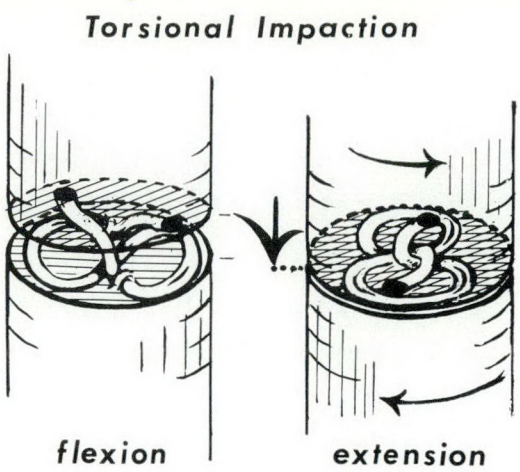

Fig. 1.—Forces acting at the articular surface of the right knee, femur rotating medially and tibia laterally, seen from in front. As the knee passes from flexion to extension the femur rotates internally on the tibia—the "screw-home" effect. In extension, this twists the anterior cruciate ligament about the posterior and shortens these ligaments, bringing tibia and femur together. This motion not only apposes the articular surfaces but transfers the horizontal twisting to the articular surface. The entire process is referred to as "torsional impaction". (Reproduced by permission from HELFET AJ: *Management of Internal Derangements of Knee,* Philadelphia, Lippincott, 1963, p 12.)

walking dissects the centre from the main epiphysis and fractures the articular cartilage, and eventually a loose body forms. We believe that in the majority of patients osteochondritis dissecans develops on a preexisting anomalous centre of ossification, and that the torsional impaction associated with walking leads to avascularity and subsequent separation.

In our experience, knees with osteochondritis dissecans frequently have associated congenital anomalies, such as genu recurvatum, loose patellas, and lax collateral ligaments. These knees tend to be unstable and exaggerate the normal forces acting at the knee and increase the chance of injuring the anomalous centre and forming an osteochondral fragment.

METHOD OF STUDY

In this study, we assessed 80 knees in 61 patients with osteochondritis dissecans. The cases were obtained through the record departments of the Montreal General Hospital and Montreal Children's Hospital and from the records of members of the attending staff at these institutions. Twenty patients were interviewed and examined by the authors; the remainder had been examined by members of the attending staff at the respective hospitals. We excluded transchondral fractures from the study because they result from acute trauma which provokes violent twisting of the knee and subluxation or dislocation of the patella.

RESULTS

These 80 knees were divided into four separate groups according to their management. For each patient, the individual surgeon selected the treatment.

Conservative Treatment (30 Patients)

This group, 18 males and 12 females, contained 47 knees (Table I). In 17 patients between 7 and 18 years of age both knees were involved. In them, the average duration of treatment was four months—a range of two months to one year. The symptomatic knee was placed in a long-leg cylinder with the knee flexed to varying degrees. Usually weight bearing was allowed but the results of treatment were the same when the patient bore his full weight, partial weight, or no weight at all. In 28 patients, the lesion was over the medial femoral condyle, in 15, both knees were involved. In two patients, there was a lesion over the lateral femoral condyle in both knees. Twenty-eight patients had no symptoms at follow-up—four months to 10 years after conservative treatment. Two lesions separated after treatment in a long-leg cylinder (Cases 2 and 14). In Case 2, the fragment was extracted and 14 months later the patient had no symptoms, although the medial femoral condyle appeared to be flattened on the radiograph. In the other patient (Case 14), the fragment was fixed back into its bed; the patient had no symptoms three years later and his films appeared normal.

Excision (11 Patients)

These patients were between 12 and 25 years of age. In this procedure we removed

TABLE I.—Conservative Treatment. Results in 30 Patients

No.	Name	Sex	Age (years)	Location*	Follow-up	Duration of treatment	Results	Radiograph
1	M.L.	M	13	MFC (bilat.)	1 yr.	4 mos.	Asymptomatic	Normal
2	J.F.	F	9	MFC	1 yr.	4 mos.	Detached	Flattening
3	S.L.	F	16	MFC	18 mos.	6 wks.	Asymptomatic	Normal
4	K.M.	M	17	MFC	1 yr.	4 mos.	"	"
5	F.U.	M	7	LFC (bilat.)	3 yrs.	2 mos.	"	"
6	J.N.	F	13	MFC "	2 yrs.	6 mos.	"	"
7	P.I.	F	12	MFC	6 yrs.	4 mos.	"	"
8	L.J.	F	10	MFC (bilat.)	4 yrs.	4 mos.	"	"
9	T.N.	M	15	MFC "	3 yrs.	6 mos.	"	"
10	J.D.	M	12	MFC "	2 yrs.	4 mos.	"	"
11	D.R.	M	13	MFC "	2 yrs.	2 mos.	"	"
12	D.G.	M	12	MFC "	3 yrs.	2 mos.	"	"
13	S.R.	M	13	MFC "	10 mos.	2 mos.	"	"
14	F.K.	M	18	MFC "	3 yrs.	5 mos.	Detached	"
15	L.A.	M	16	MFC "	5 yrs.	4 mos.	Asymptomatic	"
16	B.J.	M	15	MFC "	10 yrs.	1 yr.	"	"
17	M.C.	F	12	MFC	3 yrs.	6 mos.	"	"
18	M.F.	F	16	MFC (bilat.)	2 yrs.	4 mos.	"	"
19	C.R.	M	11	MFC	2 yrs.	4 mos.	"	"
20	D.C.	F	10	MFC	3 yrs.	3 mos.	"	"
21	O.O.	F	12	LFC (bilat.)	4 yrs.	3 mos.	"	"
22	C.O.	M	13	MFC "	3 yrs.	3 mos.	"	"
23	D.C.	M	15	MFC "	4 yrs.	4 mos.	"	"
24	Y.O.	F	10	MFC	1 yr.	3 mos.	"	"
25	L.D.	F	12	MFC	6 mos.	4 mos.	"	"
26	O.C.	M	11	MFC (bilat.)	8 mos.	2 mos.	"	"
27	L.P.	M	12	MFC	2 yrs.	6 wks.	"	"
28	A.C.	M	13	MFC	1 yr.	3 mos.	"	"
29	S.L.	F	9	MFC	4 mos.	3 mos.	"	"
30	B.J.	M	8	MFC	1 yr.	4 mos.	"	"
			Average		Average	Average	28	29
		18 M 12 F	12.5	28 MFC 2 LFC	2.5 yrs.	4 mos.	asymptomatic	normal

*MFC = medial femoral condyle; LFC = lateral femoral condyle.

the osteochondral fragment from its bed on the articular surface of the medial femoral condyle in seven males and four females (Table II). At follow-up five months to six years later, eight patients had no symptoms. Three had some symptoms in the knee with occasional mild pain and swelling after exercise (Cases 35, 36 and 41). No patient had any limitation of general activity. The radiographs of two of the three symptomatic patients showed early degenerative osteoarthritis of the medial femoral compartment. One of the patients without symptoms had a similar result (Case 38). The radiographs of an asymptomatic patient are shown in Fig. 2.

TABLE II.—Excision. Results in 11 Patients

No.	Name	Age (years)	Sex	Location*	Follow-up	Results	Radiograph
31	M.T.	14	M	MFC	1 yr.	Asymptomatic	Normal
32	J.N.	13	F	MFC	8 mos.	"	"
33	K.S.	12	F	MFC	1 yr.	"	"
34	G.K.	25	M	MFC	6 yrs.	"	"
35	R.G.	20	F	MFC	1 yr.	Pain	"
36	R.B.	19	M	MFC	1 yr.	"	Irregularity
37	D.D.	18	F	MFC	6 mos.	Asymptomatic	Normal
38	L.A.	16	M	MFC	5 mos.	"	Irregularity
39	D.C.	18	M	MFC	1 yr.	"	Normal
40	E.R.	14	M	MFC	2 yrs.	"	"
41	M.D.	14	M	MFC	2 yrs.	Pain	Irregularity
		Average 17.5	7 M 4 F	11 MFC	Average 2 yrs.	8 asymptomatic	8 normal

*MFC = medial femoral condyle.

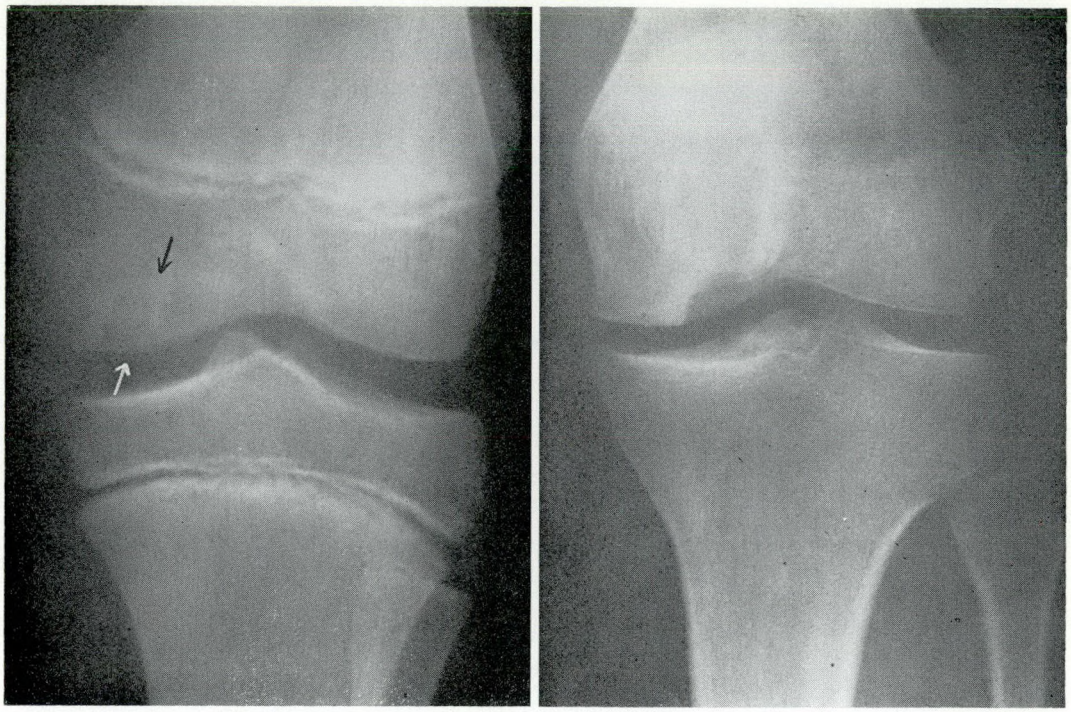

Fig. 2a Fig. 2b

Fig. 2.—Excision, Case 37. A 16-year-old youth had a one-year history of pain and occasional swelling. The osteochondral fragment was excised. (a) Anteroposterior view before operation shows the lesion on the medial femoral condyle; (b) anteroposterior view five years after operation.

Extraction (14 Patients)

These patients were treated by removing the osteochondral fragment as it lies loose in the joint cavity. Nine were males and five females (Table III). They were between 9 and 30 years of age. The medial femoral condyle was involved in 12, the lateral condyle in two. At follow-up, two months to five years later, 11 patients had no symptoms and had clinically normal knees. Three knees produced symptoms; two gave pain occasionally during vigorous activity or long standing (Cases 42 and 51). The knees appeared normal clinically. The third patient had occasional pain and

TABLE III.—Extraction. Results in 14 Patients

No.	*Name*	*Age (years)*	*Sex*	*Location**	*Follow-up*	*Clinical result*	*Radiograph*
2	J.F.	9	F	MFC	14 mos.	Asymptomatic	Some flattening
42	G.M.	14	M	MFC	3 yrs.	Occasional discomfort	Slight roughening
43	P.S.	14	F	MFC	2 yrs.	Asymptomatic	Normal
44	R.M.	15	F	LFC	2 yrs.	"	"
45	L.A.	30	M	MFC	5 yrs.	"	Some flattening
46	R.H.	20	M	MFC	4 yrs.	"	Normal
47	G.L.	25	M	MFC	8 mos.	"	"
48	M.C.	17	F	MFC	1 yr.	Crepitus and occasional pain	"
49	D.B.	17	M	MFC	3 yrs.	Asymptomatic	"
50	J.A.	23	M	MFC	2 mos.	"	"
51	R.O.	19	M	MFC	5 yrs.	Occasional pain	"
52	S.Q.	18	M	MFC	2 yrs.	Asymptomatic	"
53	G.S.	23	M	LFC	1 yr.	"	"
54	R.P.	29	F	MFC	5 yrs.	"	Early osteoarthritis
		Average 19.5	9 M 5 F	12 MFC 2 LFC	Average 2.4 yrs.	11 asymptomatic	10 normal

*MFC = medial femoral condyle; LFC = lateral femoral condyle.

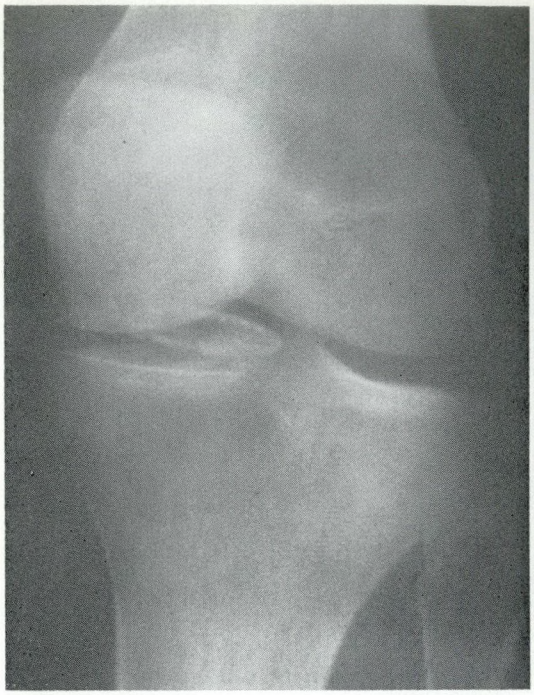

Fig. 3a

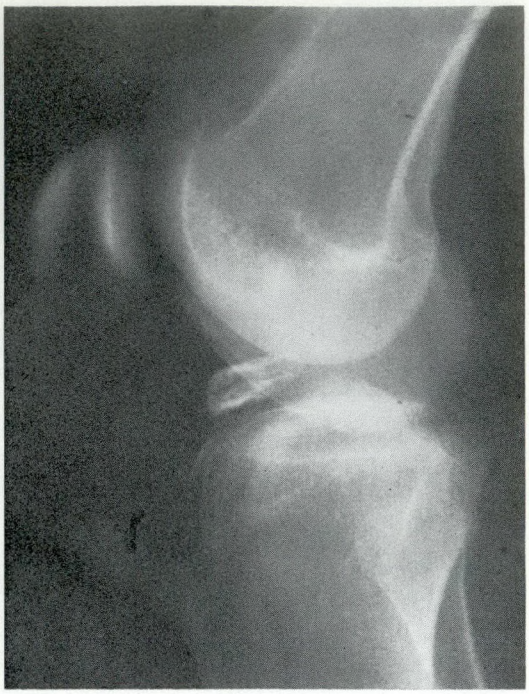

Fig. 3b

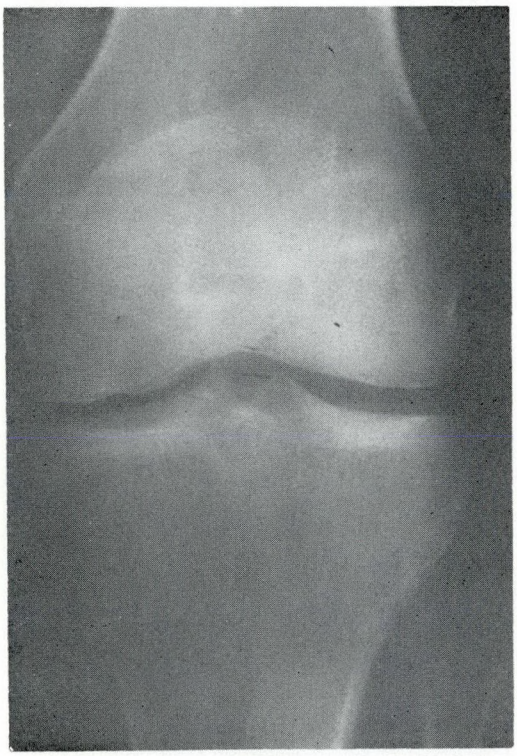

Fig. 3c

some limitation of activity; on examination, the knee had palpable crepitus and slight effusion (Case 48). In two patients with no symptoms, the knee showed some flattening of the medial femoral condyle; a third asymptomatic knee had a slight irregularity at the site of the lesion (Cases 2, 45 and 54). The knee of Case 45, asymptomatic at five-year follow-up, is shown in Fig. 3.

Fixation (8 Patients)

In this procedure the osteochondral fragment is fixed to its bed using small bone pegs.[8] If the osteochondral fragment lies in its bed, the fragment is drilled with a 7/64-inch drill bit and the fragment fixed to the subchondral bone with the small bone pegs (usually two per fragment). If the fragment is loose and can be fitted into

Fig. 3.—Extraction, Case 45. A 30-year-old man had a six-month history of a loose fragment, which was later extracted; (a) anteroposterior view before operation, (b) lateral view before operation and (c) anteroposterior view five years after operation. Note the irregularity of the medial femoral condyle.

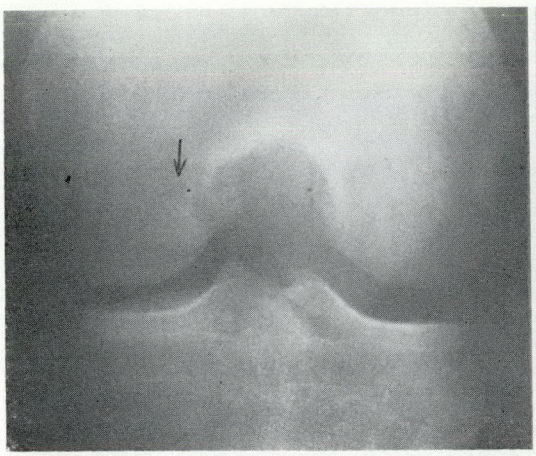

Fig. 4a

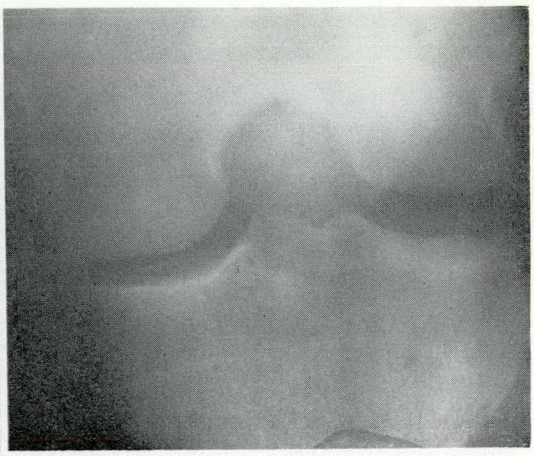

Fig. 4b

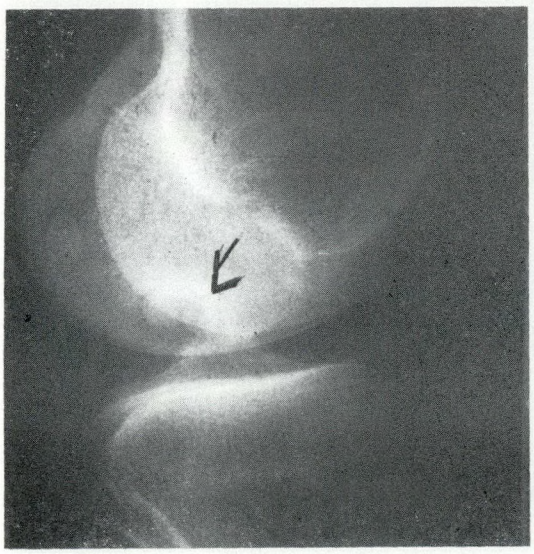

Fig. 4c

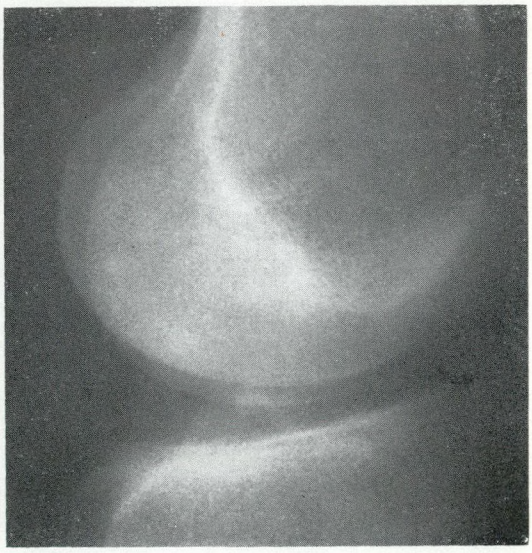

Fig. 4d

Fig. 4.—Fixation, Case 60. This 20-year-old man had a three-month history of pain. The fragment was fixed *in situ* with autogenous bone pegs; (a) tunnel view before operation, (b) tunnel view three years after operation, (c) lateral view before operation, and (d) lateral view three years after operation.

its bed without producing a prominence, bone pegs are inserted; if not, the fragment is extracted. The pegs, cortical bone of matchstick thickness about 2 cm. long, are obtained from the subcutaneous border of the medial aspect of the proximal tibial metaphyses; banked homologous bone can also be used. Eight patients had this procedure (Table IV). These patients—five men and three women—had an average age of 20 years (range 17 to 23). In all, the medial femoral condyle was involved. In two, the fragment was loose and was reduced and fixed with the bone peg; in the other six, the fragment was pegged *in situ*. After a follow-up of from eight months to three years, all patients were asymptomatic and radiographs were normal. The radiographs of a typical knee are shown in Fig. 4.

Associated Lesions

In these 61 patients (80 joints), 33 joints had an arthrotomy. Associated lesions consisted of six torn medial menisci, one torn lateral meniscus, and five subluxating

TABLE IV.—Fixation. Results in Eight Patients

No.	*Name*	*Age (years)*	*Sex*	*Location**	*Follow-up*	*Clinical result*	*Radiograph*
14	F.K.	18	M	MFC	3 yrs.	Asymptomatic	Normal
55	R.G.	22	M	MFC	8 mos.	"	"
56	R.C.	19	F	MFC	2 yrs.	"	"
57	R.K.	20	M	MFC	3 yrs.	"	"
58	T.R.	21	F	MFC	1 yr.	"	"
59	R.S.	23	M	MFC	2 yrs.	"	"
60	L.D.	20	F	MFC	3 yrs.	"	"
61	E.C.	17	M	MFC	1 yr.	"	"
		Average 20	5 M 3 F	8 MFC	Average 1.9 yrs.	8 asymptomatic	8 normal

patellas with early chondromalacia of the patella. The osteochondral lesions probably represent the result of ligamentous instability which increases the normal torsional forces on the knee. Probably more of these patients (than the five noted) had subluxating patellas because it was not looked for in all. As noted above, we did not demonstrate anomalous centres in any of these patients.

Discussion

Osteochondritis dissecans in the adolescent is managed differently from that in the adult. If this lesion arises in an anomalous centre of ossification in the femoral epiphyseal centre, its natural history, usually one of spontaneous healing, becomes easier to understand. A long-leg cylinder, recommended by Green and Banks,[9] will protect the knee from torsional stress. In most of our patients (28 of 30 patients or 45 of 47 knees), the lesion healed with complete recovery. Occasionally healing is delayed, probably because the anomalous centre separates completely from its subchondral bed before treatment begins.

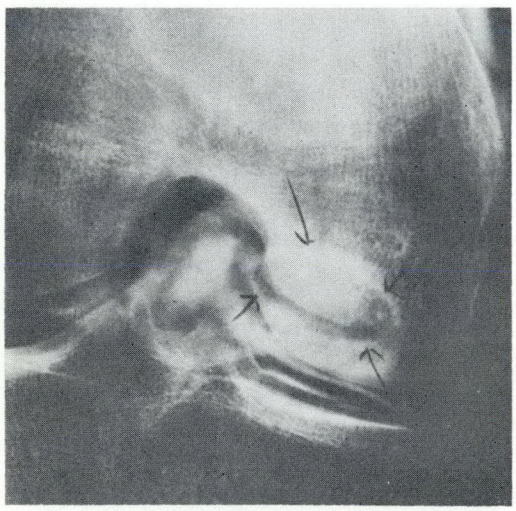

Fig. 5.—Arthrogram of a knee with osteochondritis dissecans of the medial femoral condyle. The contrast medium has penetrated between the osteochondral fragment and its base. This lesion would probably not heal spontaneously.

Recently we have begun to assess patients with osteochondritis dissecans by arthrography, a technique described by Almgard and Wikstad in 1964.[10] Fig. 5 shows that the contrast medium penetrates between the osteochondral fragment and its bed, suggesting that this lesion would not heal spontaneously. The arthrogram may be valuable in predicting prognosis before one chooses conservative therapy. As long as the fragment remains in its bed, however, and the distal femoral epiphyseal line has not closed, conservative therapy is usually successful.

When the femoral epiphyseal line has closed, spontaneous healing is much less likely. The lesion is less common at this age, but, from our results, we believe that drilling and pegging the fragment (fixation) is justified. This procedure, unlike insertion of the Smillie nail, does not require subsequent arthrotomy for removal.[6] So far such pegging has been successful in all eight patients in this group although our follow-up is short. The alternative, excision, has in our series been associated with subsequent degenerative changes in three of 11 patients (two symptomatic).

The management of the loose fragment is less clear. Usually, the fragment changes its shape considerably after breaking off from the articular surface. The cartilage component, which is nourished by synovial fluid, increases in size and when replaced

in its bed creates a prominence. In these patients, the fragment should probably be extracted. Drilling the defect on the femoral articular surface is reported to help by accelerating replacement of the defect by fibrocartilage.[11] Degenerative osteoarthritis commonly follows this form of treatment. Occasionally, however, if the fragment is trimmed, it can be replaced in its bed and the articular contour restored. We have not done such trimming and replacement often enough to draw any definitive conclusions.

Summary

In the knee, an anomalous centre of ossification may predispose to osteochondritis dissecans. In the adolescent, this lesion seems to heal spontaneously.

The forces in the normal knee, especially when intensified by a ligamentous laxity, may induce horizontal cleavage, dissection of an osteochondral fragment, avascular necrosis, and subsequent loose-body formation. In this process, torsional impaction is probably the primary force.

An arthrogram often detects patients with osteochondritis dissecans in whom there is horizontal cleavage of the articular cartilage.

Before the distal femoral epiphysis has closed and especially before horizontal cleavage appears, immobilization in a long-leg cylinder induces healing.

Where possible the osteochondral fragment should be fixed with bone pegs rather than by metallic fixation; this treatment is better than either excision or extraction.

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Résumé

Dans le genou, un centre anormal d'ossification peut prédisposer à l'ostéochondrite disséquante. Chez l'adolescent, cette lésion semble évoluer vers la guérison spontanée.

Les forces mécaniques qui agissent sur le genou normal, surtout quand elles sont intensifiées par une certaine laxité des ligaments, peuvent provoquer un clivage horizontal, la dissection d'un fragment d'ostéo-cartilage, une nécrose avasculaire et subséquemment la formation d'un corps étranger. Dans ce processus, l'impact de torsion est probablement la force primaire en cause.

Un arthogramme permet souvent de découvrir des malades souffrant d'ostéochondrite disséquante, chez lesquels existe un clivage horizontal du cartilage articulaire.

Avant la fermeture de l'épiphyse fémorale distale et surtout avant l'apparition du clivage horizontal, l'immobilisation dans un cylindre de la longueur de la jambe favorise la guérison.

Quand la chose est possible, on devra fixer le fragment ostéocartilagineux par des chevilles osseuses plutôt que par des prothèses métalliques. Ce traitement est préférable à l'excision ou à l'extraction.

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DIVERTICULITIS OF THE VERMIFORM APPENDIX

D. A. AUBREY, M.B., M.S., F.R.C.S.,* *Cardiff, Wales*

THIS report describes a patient with appendicular diverticulitis and briefly reviews the relevant literature.

CASE REPORT

A previously healthy 22-year-old man complained of pain of 18 hours' duration in the right iliac fossa. He had no other symptoms. Since there was tenderness and local muscular rigidity in that area, emergency appendectomy was done and an acutely inflamed appendix removed. Postoperative recovery was uneventful.

In its distal one-half, the musculature of the appendicular wall was thickened and, extending through its whole thickness, there was a narrow "false" diverticulum (Fig. 1). The latter was lined by granulation tissue and there was an acute inflammatory reaction in the surrounding muscularis and serosa, although elsewhere the appendix was normal. The pathological diagnosis was acute appendicular diverticulitis.

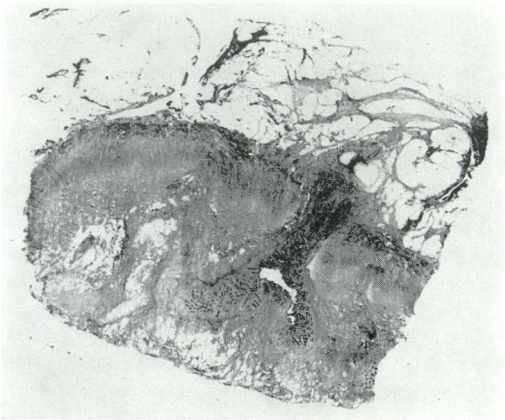

Fig. 1.—Section of the vermiform appendix showing the collapsed false diverticulum penetrating through the hypertrophied muscle coats (original magnification × 10).

DISCUSSION

The incidence of appendiceal diverticula is about 0.5%[1-4] (0.08%[5] to 2.8%[6]), the condition being commonest in the fourth decade.[5] A solitary diverticulum is commoner than multiple ones[4] and the mesenteric aspect of the distal part of the appendix is most frequently affected.[5, 7] The uncomplicated condition is sometimes recognized radiologically,[7-9] but this investigation often fails to demonstrate it when the appendix is obstructed at its cecal end.[1, 3] Most patients present either with acute appendicitis,[3, 7] or with a mass in the right iliac fossa;[1, 7] usually they have experienced vague symptoms for many years.[3, 10]

Although "true" and "false" diverticula may be distinguished histologically,[1, 3, 7] this distinction is rarely possible at operation.[5] The condition predisposes to acute appendicitis with early perforation[2, 5]—which is not surprising because most diverticula are merely mucosal herniations—and the advanced inflammatory changes often make even simple identification of the diverticulum difficult or impossible.[5] Thus, the appendix may simply disappear into an inflammatory mass,[7] or be surrounded by a granuloma after diverticular perforation into the mesoappendix.[2] These "hidden" diverticula can simulate carcinoma, and right hemicolectomy has been done unnecessarily for the condition.[7] Clearly this should be avoided if possible. If, therefore, at operation, there is a mass of dubious etiology in the right iliac fossa, and an infective lesion such as a hidden appendiceal diverticulum is a possibility, the surgeon may simply drain the area, administer antibiotics and re-explore after a short interval, when the condition might be more obviously benign and appendectomy safely performed.

Because appendicular diverticula predispose to perforative appendicitis,[2, 5] appendectomy should be advised if the uncomplicated condition is found incidentally, i.e. radiologically. Furthermore, because chronic and "healed" perforative appendicitis are potent factors in the pathogenesis

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of the condition,[1, 5, 11-13] appendectomy should be performed expeditiously in these conditions, so as to forestall diverticular formation.

Summary

Because "hidden" appendicular diverticulitis can mimic carcinoma, it is important to be aware of this uncommon condition. If the lesion is suspected as the cause of a mass in the right iliac fossa, a conservative surgical approach seems preferable to emergency right hemicolectomy. Appendectomy is indicated for the uncomplicated condition to prevent acute perforative appendicitis. Diverticulum formation may follow chronic and "healed" appendicitis, hence prompt appendectomy is advisable in these conditions.

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Résumé

Dans l'examen histologique de l'appendice chez un jeune homme de 22 ans une diverticulite appendiculaire a été diagnostiqué. La littérature relative à cette pathologie peu fréquente indique qu'une diverticulite appendiculaire "latente" peut créer une masse dans la fosse iliaque droite et simuler une tumeur néoplastique. Si le chirurgien soupçonne cette pathologie, il devra envisager un traitement chirurgicale conservateur plutôt que de recourir d'emblée à une hémicolectomie droite d'urgence. Pour prévenir une appendicite perforée, l'appendicectomie est indiquée dans les cas sans complication. Comme la formation du diverticule peut être la conséquence d'une appendicite chronique "refroidie", l'appendicectomie d'urgence est alors indiquée.

IMPORTANT NOTICE

Effective July 1, 1971, the Editorial Office of *The Canadian Journal of Surgery* will be located at **530 Scarlett Road, Suite 1002, Weston 626, Ontario.** All communications to the Editor and Editorial Department should be sent to the new address.

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HYDROLYSIS OF STILBESTROL DIPHOSPHATE BY THE ACID PHOSPHATASE OF THE BLADDER MUCOSA*

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Kingston, Ont.

In addition to the acid phosphatase found in the prostate gland, the bladder mucosa also contains measurable amounts of this enzyme, the function of which has not been determined. Some bladder carcinogens are detoxified in the liver by conjugation to the phosphate or glucuronide, and excreted into the enterohepatic circulation and urine. Since urinary stasis is found in some patients with bladder carcinoma, it is of interest to determine if hydrolysis (deconjugation) occurs *in vivo*. During a recent investigation, we noted that after an intravenous injection of stilbestrol diphosphate, some hydrolysis of this compound occurred in the bladder wall. We therefore elected to study the fate of a solution containing tritiated stilbestrol diphosphate instilled into the isolated urinary bladder of rabbits.

Because stilbestrol is ether soluble and stilbestrol diphosphate is water soluble, its radioactivity, and therefore the extent of its hydrolysis, can be determined in each fraction. In this experiment hydrolysis was measured in the instilled solution, in homogenates of the bladder wall, and in the venous blood from the bladder.

Material and Methods

Twenty adult male rabbits, weighing an average of 4 kg., were anesthetized with intravenous pentobarbital (Nembutal) supplemented by open ether. The bladder was exposed through a midline abdominal incision, and the lower ureters were isolated and ligated at their entrance into the bladder. The bladder was catheterized, emptied by manual expression, and washed three times with 10 ml. of acetate buffer (pH 5.0 at 38° C.). The test solution, containing approximately 0.057 mg. of tritium-labelled diethylstilbestrol diphosphate sodium (4 μc. in 20 ml. acetate buffer), was instilled through a No. 20 needle inserted into the mid-point of the urethra and guided into the bladder. The urethra was then ligated above the point of injection, the bladder was tested for leakage, returned to the peritoneal cavity and the skin incision closed. The urethra was ligated at the bladder neck. The anatomy of the rabbit differs from that of the human or dog, and we are certain that no prostatic secretions entered the bladder during the experiment. While acid phosphatase can be demonstrated in the bladder mucosa, the whole purpose of this study was to demonstrate that the acid phosphatase in the bladder mucosa could hydrolyze a suitable substrate.

To determine the rate of absorption of the instilled solution, four rabbits were sacrificed at 15 and 30 minutes, and at one, two and four hours. Immediately before death, we obtained a sample of blood from the vesical veins by ligating all the tributaries of the iliac vein, except those draining the bladder, and aspirating blood from the iliac vein. Simultaneously a sample of blood was obtained by cardiac puncture. The rabbit was killed by air embolism, the bladder excised and the volume of the recovered solution measured —invariably this was $\pm$ 0.5 ml. of the instilled volume. The bladder was then washed five times with 5-ml. portions of acetate buffer and prepared for analysis. Representative samples from the recovered solution, including bladder washing, bladder wall and serum, were prepared for liquid scintillation counting.

We used two methods to prepare the tissues for counting: (1) the hyamine-hydroxide toluene method measures the total radioactivity (water-soluble plus ether-soluble components), and (2) the ether extraction-toluene phosphor method measures the ether-soluble radioactive components (diethylstilbestrol).[1]

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We used established techniques[1] to measure the activity in the various solutions. However, in measuring the ether-soluble components in the recovered bladder solutions, we made one modification: the solutions were immediately added to 5 ml. of cold ether (5° C.) in centrifuge tubes, shaken to inhibit further enzyme action and centrifuged. Further ether extraction continued as described elsewhere.[1]

The rate of absorption from the bladder was determined by measuring the radioactivity that remained in the bladder solution. These measurements were made at intervals which allowed for partial disappearance (e.g. 20% to 70%) of the radioactive material. The results were expressed as a percentage of the total instilled compound that had been absorbed in that time.

Results

After instilling 4 μc. of ^{3}H stilbestrol diphosphate in 20 ml. of acetate buffer into the isolated rabbit bladder, there is a rapid loss of radioactivity with time (Fig. 1), which is not accounted for by loss of volume because $\pm$ 0.5 ml. of the initial solution was recovered. At 30 minutes, only 70% of the initial radioactivity can be recovered from the bladder solution (Fig. 1). At this time, extensive hydrolysis of the stilbestrol diphosphate had occurred, because 45% of the initial radioactivity was now ether soluble, leaving 25% in the water-soluble phase (stilbestrol diphosphate). Absorption accounted for the remaining 30% of the radioactivity.

During the first two hours, loss of radioactivity proceeds rapidly because at the end of this time only 30% of the initial activity remained in the bladder solution. After two hours, absorption (loss of radioactivity) markedly decreases, and between two and four hours only an additional 10% is absorbed.

When the log. of total radioactivity (^{3}H stilbestrol diphosphate plus ^{3}H stilbestrol) remaining in the bladder solution over the first two hours is plotted against time, a straight line is obtained. During the period of maximal stilbestrol transfer, the absorption of the compound follows first-order kinetics (the absorption of a compound per unit of time is directly proportional to its concentration).[2]

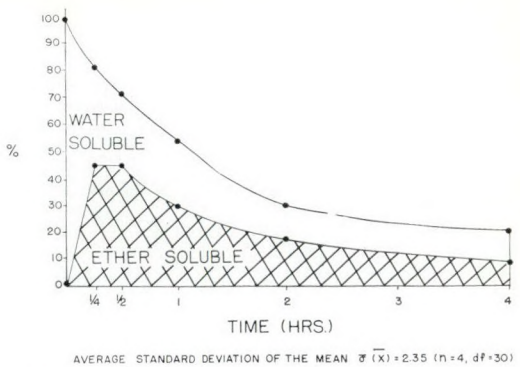

Fig. 1.—Percentage of instilled radioactivity recovered from the bladder solution over a four-hour period.

To confirm that the radioactivity in the ether-soluble fraction was free stilbestrol, the recovered solutions were tested by the Dryer method[3] of colourimetric chemical analysis—a method applicable only to samples that contain large quantities of stilbestrol (0.125 to 0.005 mg.). Aliquots of bladder solution taken at 15 and 30 minutes, and one and two hours, contained .024, .020, .012 and .005 mg. of stilbestrol respectively. Bladder-wall and blood samples contained quantities too small for analysis. We found that the samples of bladder wall that had been exposed to the radioactive solution for the shortest periods (15 and 30 minutes) contained the greatest quantity of radioactivity (Fig. 2). In

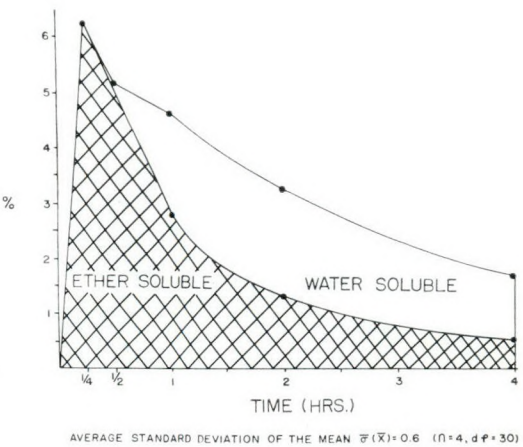

Fig. 2.—Percentage of instilled radioactivity recovered from the bladder wall over a four-hour period.

addition, all the radioactivity in the bladder-wall samples taken at that time was ether soluble (stilbestrol). The recovered activity at this peak period was 5% to 6% of that initially instilled. The ether-soluble fraction in the bladder wall dropped sharply during the first hour, and a more gradual decrease occurred until, at four hours, only 0.4% of the activity initially instilled was recovered from the bladder. After reaching a peak at 15 minutes, both the water-soluble and ether-soluble radioactivity dropped with time. Therefore apparently no stilbestrol diphosphate or stilbestrol was deposited intramurally.

To determine the absorption of stilbestrol or stilbestrol diphosphate, we subtracted the amount of radioactivity in the cardiac samples from that in the vesical serum. The maximal radioactivity in the vesical veins occurred 30 minutes after the experiment began (Fig. 3). Most of the

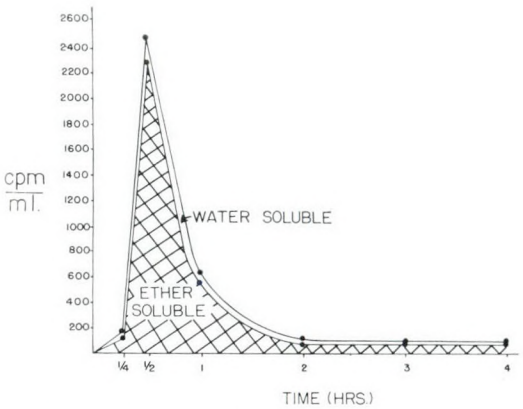

Fig. 3.—Radioactivity in venous-arterial serum after instillation of ^{3}H stilbestrol diphosphate in rabbit bladder.

activity leaving the bladder was found in the ether-soluble fraction, which suggests that the lipid-soluble ^{3}H stilbestrol is preferentially absorbed, or, less likely, that it is converted outside the bladder.

The product of the integrated area under the curve (Fig. 3) is the overall difference of radioactivity in the venous and arterial systems. By calculating this area and multiplying it by the approximate flow rate (13 ml./min.) in the cannulated internal iliac vein, we determined that the total amount of radioactivity absorbed into the vesical veins was 1.10 x 10^{6} cpm (counts per minute) over the four-hour period. Initially 1.65 x 10^{6} cpm was instilled into the bladder as ^{3}H stilbestrol diphosphate. Therefore 67% of the radioactivity was transported from the bladder by the vesical veins. At four hours only 20% of the radioactivity remained in the bladder solution (Fig. 1) and 1.6% in the bladder tissue (Fig. 2). Thus we could account for 89% of the initial instilled radioactivity. The results obtained were consistently reproducible. The spread of data as measured by the average standard deviation of the mean (Figs. 1 and 2) was low compared with the trends established.

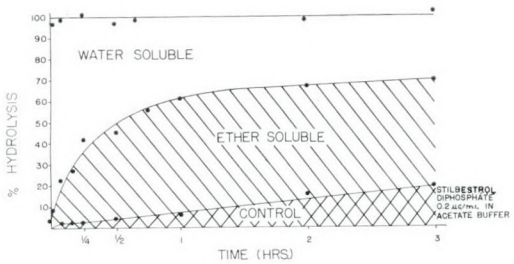

Fig. 4.—Hydrolysis of ^{3}H stilbestrol diphosphate by the enzyme in the acetate buffer which had been instilled into the isolated bladder for one hour.

To determine if the acid phosphatase hydrolyzed the stilbestrol diphosphate in the bladder mucosa or in the instilled solution, 20 ml. of the acetate buffer was instilled into the isolated rabbit bladder. At the end of one hour the solution was removed and placed in a beaker in a water bath at 37° C. To this was added 4 μc. of ^{3}H stilbestrol diphosphate in 0.1 ml. of acetate buffer. Samples of this solution were taken at various times to determine the extent of ^{3}H stilbestrol diphosphate hydrolysis. The total concentration of radioactivity (water- plus ether-soluble components) remained constant, but the composition of the solution changed. The stilbestrol diphosphate was rapidly hydrolyzed (Fig. 4), indicating that large quantities of the enzyme migrated or were leached out into the buffered solution. Hydrolysis was markedly inhibited after one hour.

Discussion

Our results show that tritiated stilbestrol diphosphate instilled into the isolated rabbit bladder was rapidly hydrolyzed to free stilbestrol, which was then absorbed. The rate of absorption was rapid but of short duration. In the first half-hour the ether-soluble radioactivity (free stilbestrol) in the bladder solution, bladder wall, and venous blood reached a maximum (Figs. 1-3). At the end of one hour, only 54% of the radioactivity that had been instilled into the bladder could be recovered (Fig. 1). It appeared that a barrier must be overcome before absorption occurs, and that a similar barrier operates once the concentration of the compound falls below a certain level.

If the concentration of ^{3}H stilbestrol in the bladder solution were kept constant, the absorption from the bladder would probably remain constant. However, in this experiment the radioactivity in the bladder solution decreased with time. The rate at which ^{3}H stilbestrol diphosphate was converted to ^{3}H stilbestrol by enzyme hydrolysis probably also decreased with time. In an *in vivo* experiment (Fig. 4) we showed that such a decrease occurred and is probably caused by some inhibitory mechanism.

During the period of maximal absorption (15 to 30 minutes) most of the activity in the bladder tissue and the venous blood was ether soluble (Figs. 2 and 3). There appeared to be no deposition of ^{3}H stilbestrol in the bladder wall because the radioactivity decreased with time. Only 0.4% of the instilled activity was found in the bladder wall at four hours as free ^{3}H stilbestrol.

Since the lipid-soluble metabolite was preferentially absorbed, the enzyme, acid phosphatase, played a vital but indirect role in absorption of stilbestrol. However, the pH and temperature must be controlled before enzyme activity can begin. In three instances where the bladder containing the instilled solution was allowed to cool for two hours, there was negligible hydrolysis. The pH of the solution, in addition to affecting enzyme activity, also affects the permeability of the bladder wall to certain ions.[2, 4] The optimal pH for enzyme activity in man does not necessarily coincide with the pH necessary for maximal absorption of the product of the enzyme action. The lipid solubility of the product is an important factor in absorption. Numerous reports on the mechanism of drug absorption and secretion across cell membranes indicate that the capacity of chemicals to traverse the membranes is to a great degree a function of their lipid solubility. Thus products of enzyme action that are soluble in lipids at the correct pH are absorbed.

Summary

Experiments were designed to determine the extent of hydrolysis of ^{3}H stilbestrol diphosphate instilled into the isolated rabbit bladder.

Animals were sacrificed at 15 and 30 minutes, one, two and four hours after instillation of the solution (4 μc. in 20 ml. of acetate buffer). The radioactivity in recovered solutions, bladder tissue and serum samples was counted using liquid scintillation techniques. At 30 minutes, only 70% of the initial radioactivity can be recovered from the bladder and 45% hydrolysis had occurred. This loss of radioactivity which represented absorption (since there was no loss in volume) continued rapidly for the first two hours. The radioactivity in the bladder wall, and the venous blood draining the bladder, reached a peak within the first 30 minutes, and was all in the hydrolyzed form (free stilbestrol). We found that approximately 67% of the radioactivity initially instilled was transported from the bladder by the vesical veins. At four hours, only 20% of the radioactivity remained in the bladder solution, and 1.6% in the bladder tissue.

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Résumé

Etant donné que des malades atteints de cancer vésical souffrent de stase urinaire, nous avons décidé d'établir le point de savoir si le diphosphate de stilboestrol marqué au tritium est déconjugué *in vivo*. Nous avons donc instillé ce composé dans la vessie isolée de lapin, à raison de 4 μc de ^{3}H diphosphate de stilboestrol dans 20 ml d'un tampon à l'acétate. Nous avons alors mesuré la radio-activité dans les solutions récupérées, dans le tissue vésical et dans des échantillons de sérum, utilisant à cette fin la technique de scintillation en milieu liquide. Nous avons constaté que 30 minutes après instillation du composé marqué, on ne récupérait que 70% de la radio-activité initiale dans les solutions instillées et que l'hydrolyse s'était produite à concurrence de 45%. Dans la paroi de la vessie et la veine vésicale, la radio-activité atteignait un sommet à 30 minutes, période à laquelle le produit était complètement hydrolysé.

Nous concluons que le diphosphate de stilboestrol marqué au tritium subit l'hydrolyse ou la déphosphorylation sous l'action de la phosphatase acide de la vessie et que la muqueuse absorbe de préférence le stilboestrol liposoluble libre.

CARCINOMA OF URETER

Ureteral carcinoma accounts for 1% of all carcinoma of the upper urinary tract. The prognosis of carcinoma of the ureter has been evaluated generally as poor, possibly because of the thinness of the ureteral wall and its rich lymphatic drainage system, which allows local invasion and metastatic spread to occur at a relatively early stage. The difficulty in diagnosis and the consequently advanced stage of the disease at the time of treatment could also be implicated in the poor prognosis. The authors' study was undertaken to correlate the clinical, radiologic, and pathologic findings in 100 new cases of carcinoma of the ureter in an attempt to evaluate the factors which might provide an earlier diagnosis.

Patients were gathered from 13 different hospitals. All pertinent data were transferred to a prepared questionnaire and coded having all the tumours graded by pathologists. All instances of ureteral tumours associated with carcinoma of the kidney, the ureteral stump after nephrectomy, or of primary carcinoma of the bladder extending into the ureter were excluded. It was found that ureteral tumours occur three times more frequently in male than in female patients. The clinical findings in 102 patients were gross hematuria in 76%, frequency and dysuria 52%, colic in 50%, and other symptoms with lesser frequency. It is also of interest to note that albuminuria was found in 45% and anemia was present in 13% of the patients; pyuria was seen in 23%. Urograms were intravenously administered and 63% of the patients in whom the kidney did not visualize were associated with invasive tumour, while only 37% were non-invasive. The more anaplastic tumours had a greater percentile of decreased visualization. Retrograde pyelograms demonstrated the tumour in 80% of the patients. The ureteral catheter could not be passed by the tumour in approximately 50% of the patients.

In most carcinomas, there appears to be a close correlation between the degree of cellular anaplasia and the invasion of the tumour. The survival rates of patients with total nephroureterectomy with or without radiation, simple nephrectomy, and partial ureterectomy, or some form of kidney-conserving procedure are discussed. Overall, the five-year survival rate for 54 patients operated upon before 1963 was 42.6%.

In their discussion, the authors indicate that carcinoma of the ureter does not tend to be more malignant than a tumour of the bladder urothelium, and that its prognosis, in general, is not as poor as has been suggested previously. They also found that complete nephroureterectomy with excision of a periureteral cuff of the bladder is the most widely practised treatment for primary tumours of the ureter. The authors state that the method of surgical treatment is of secondary importance in influencing the ultimate outcome of this disease. They emphasize that the 15% of recurrent tumours in the bladder indicates the need for careful follow-up examinations even in patients who have undergone a radical operation.

This is an interesting article with much of significance to those who would treat patients with ureteral tumours. The importance of the anaplasia of the carcinoma and the degree of invasion is stressed. The importance of follow-up examinations cannot be overstressed.—Bloom NA, Vindone RA, Lytton B: Primary carcinoma of ureter; report of 102 new cases. *J Urol* 103: 590, 1970

BENIGN CYSTADENOMA OF THE PANCREAS: A CASE REPORT*

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M. I. DAVIS, M.D., F.R.C.S.[C], *Toronto, Ont.*

BENIGN cystadenoma of the pancreas is rare, making up from 2% to 10% of all pancreatic cystic lesions. At the Charity Hospital, New Orleans, only seven such tumours were seen among 2,182,427 admissions over a 27-year period.[1] At the Presbyterian Hospital, New York, three multilocular and seven papillary cystadenomas were found in 23,551 surgical specimens.

Benign cystadenoma, an encapsulated cystic epithelial neoplasm usually derived from duct epithelium, is of two types: papillary and multilocular. The latter is less common than the former.[2] It can affect any part of the pancreas but more commonly the tail and/or the body than the head.

The tumour occurs more often in women (9:1 in some series) and in the fifth and sixth decades. Symptoms are non-specific or may be absent; when present, they are usually the result of pressure of the slowly enlarging tumour on contiguous structures. The usual presenting symptoms are a mass, dyspepsia, abdominal pain and weight loss. The patients may have associated biliary tract disease (12%), diabetes mellitus (8% to 13%) and, less commonly, obesity, sterility, hypertension and thyroid dysfunction. Jaundice is an uncommon presenting symptom.[3]

This paper will describe a woman with benign cystadenoma of the head of the pancreas who had interesting and unusual symptoms and who was treated successfully by pancreaticoduodenectomy.

CASE REPORT

Mrs. R.C., a 60-year-old white woman, was first seen in the Women's College Hospital, Toronto, on March 31, 1969, with a seven-week history of general ill-health, anorexia, nausea and vomiting, abdominal cramps and some diarrhea. Two and one-half weeks before admission she noticed generalized itching and that her urine was becoming darker and her stools lighter. She became frankly jaundiced four days before admission.

On physical examination, her liver was palpable 3 cm. below the right costal margin, and a globular mass was felt at the lower margin of the liver. She was afebrile and neither the liver nor the mass was tender. A preliminary diagnosis of infectious hepatitis was made.

The laboratory findings were those of cholestatic jaundice: serum bilirubin 3.0 mg./100 ml.—conjugated 2.0 mg./100 ml. and free 1.0 mg./100 ml.—serum cholesterol 456 mg./100 ml., alkaline phosphatase 8.8 Sigma units, isocitric dehydrogenase 11.0 units/ml., serum glutamic oxaloacetic transaminase 183 units/ml., serum glutamic pyruvic transaminase over 125 units/ml., total serum proteins 7.4 g./100 ml. and electrophoresis showing slight elevation of the beta globulins. All other laboratory investigations including blood sugars and hematology were within normal limits.

With no specific treatment except bed rest and low-fat diet, the patient improved. A single-dose oral cholecystogram on April 16 did not visualize either the gallbladder or biliary tree. The double-dose oral cholecystogram performed the following day showed grossly impaired dye concentration insufficient for diagnostic purposes. Her serum bilirubin level at this time was 1.8 mg./100 ml. total with 1.2 mg./100 ml. conjugated and 0.6 mg./100 ml. free.

Tests for hepatobiliary function improved and her jaundice disappeared. She was discharged from hospital on April 26 with a diagnosis of "infectious hepatitis of the cholestatic type, or cholelithiasis". She had been taking Premarin (conjugated estrogenic substances) and Librium (chlordiazepoxide HCl) at the time of admission and was advised to discontinue them.

Weekly liver function tests were performed on an outpatient basis and continued to show gradual improvement. She remained somewhat tired. On June 9, a repeat double-dose oral cholecystogram outlined the gallbladder and showed adenomyomatosis of this organ. On June 19, an intravenous cholangiogram revealed obstruction of the lower end of the common bile duct. The common duct was

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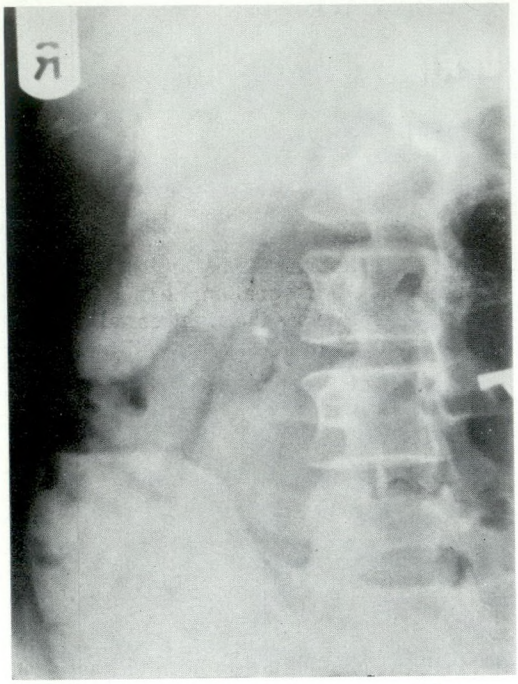

Fig. 1.—Intravenous cholangiogram. The common bile duct, cystic duct and gallbladder are grossly dilated. Note the calcification at the site of obstruction.

grossly dilated and there was a small area of calcification at the site of obstruction. The appearance of the cut-off (Fig. 1) suggested the possibility of an infiltrating neoplasm at the lower end of the common bile duct.

When readmitted on July 8, she had felt quite well for two weeks and her stools and urine were both normal. On physical examination, her gallbladder was palpable and she had a questionably palpable common bile duct. Serum cholesterol was 373 mg./100 ml. and alkaline phosphatase was 3.1 Sigma units. All other investigations were within normal limits. An upper gastrointestinal series revealed no distortion of the stomach or duodenum by the pancreas, although there was some indentation of the first part of the duodenum superiorly, suggesting enlargement of the common bile duct. Our preoperative diagnosis was "stone in the common bile duct causing partial obstruction, or carcinoma of the pancreatic head".

At laparotomy on July 11, the common bile duct was grossly dilated to approximately 2 cm. diameter. The gallbladder, which was dilated and full, did not contain any stones. A hard mass, approximately 6 cm. in diameter, involved the head of the pancreas, and this mass was surrounded by numerous thin-walled cysts measuring 1 to 1½ cm. in diameter (Fig. 2). There were several large soft lymph nodes in the surrounding area. The body and tail of the pancreas appeared normal and there was no evidence of metastases. The duodenum and head of the pancreas with the tumour were mobilized and the tumour was freed easily from the underlying superior mesenteric artery. The lesion, at this point thought to be malignant, was considered operable and pancreaticoduodenectomy was performed.

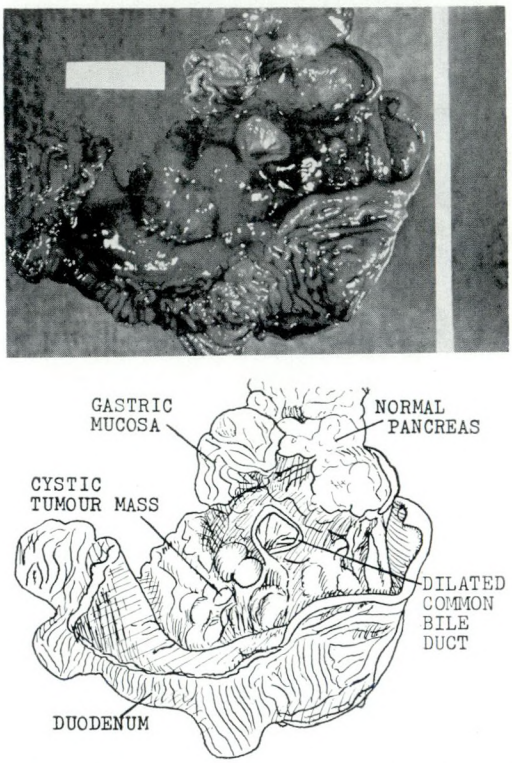

Fig. 2.—Posterior aspect of the resected specimen showing the cystic tumour within the head of the pancreas, and the dilated common bile duct entering the mass.

On microscopic examination, the tumour was a multiloculated cyst in which most of the spaces were lined by flattened cells, with a few still showing some columnar epithelium (Figs. 3 and 4). There was old hemorrhage and organization with fibrosis in the walls of the cysts and collections of lymphocytes, but no tumour showed at the resected margin of the pancreas. The lymph nodes were negative for metastases. The lesion was consistent with benign (multiloculated) cystadenoma of the pancreas, showing focal areas of degeneration.

After the operation she made a good recovery. On the fourteenth postoperative day

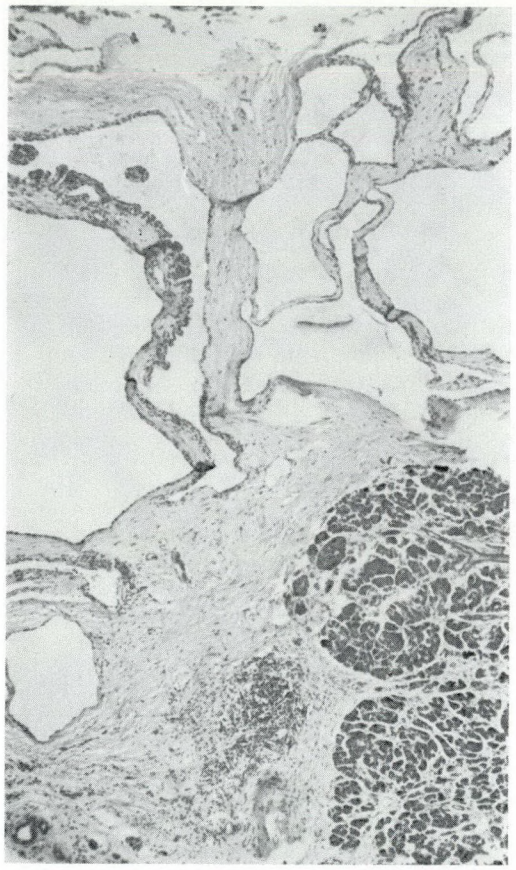

Fig. 3.—Low-power view showing multiple cysts and some normal pancreatic tissue (bottom right) (H & E × 40).

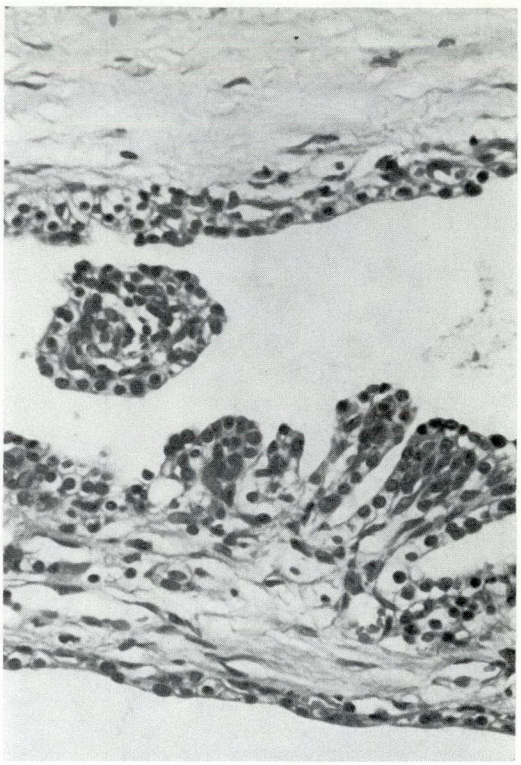

Fig. 4.—A higher-power view of the tumour. The flattened cells of the cyst tend towards columnar epithelium (H & E × 250).

her T-tube was removed, and she was discharged from hospital two days later on a full diet. Before discharge, her fasting blood sugar was 88 mg./100 ml. and a two-hour post cibum blood sugar was 134 mg./100 ml., serum amylase 50 Somogyi units/100 ml., serum cholesterol 214 mg./100 ml., alkaline phosphatase 4.1 Sigma units and serum glutamic pyruvic transaminase 25 units/ml.

She continues well and has no dietary problems.

Discussion

Jaundice, and especially an episode of jaundice which subsequently subsides, is an uncommon presenting symptom in patients with cystadenoma of the pancreas. The tumour affects the head of the pancreas in about 35% of patients, and involves the head alone in about 18.5%; in spite of this, jaundice was seen in only three of 81 patients in one series.[1] In another series[3] only two of 30 patients had jaundice. Presumably, in our patient, the presenting symptoms and the jaundice were precipitated by inflammation and edema associated with hemorrhage into a cyst, or local pancreatitis due to local pressure blocking off one of the smaller pancreatic ducts. The calcification seen on the radiograph in the region of the common duct obstruction and the histologic picture suggest that the patient had either local hemorrhage or pancreatitis. As the local edema and inflammation subsided, the obstruction was partially relieved. Clinically our patient never had a palpable pancreatic mass, but we felt the enlarged and dilated gallbladder and, probably, the common duct. She did not have diabetes mellitus and presumably this develops only when all the pancreas, or the entire tail and body, is involved. Our patient had no primary biliary tract disease and none of the other associated conditions described above.

Routine radiographs would probably not show a tumour of this size. Angiographic studies might have shown some large vessel displacement, increased vascularity in the region of the tumour and areas of decreased vascularity suggestive of cyst formation.[4] However, it seems unlikely that a definitive diagnosis could have been made by this means, especially in so small a tumour.

The operative management of these tumours depends upon their size, site and the degree of involvement of contiguous structures. If feasible, total excision is performed; if not, marsupialization or simple biopsy, with or without some form of bypass procedure is done.

The surgeon should attempt total excision, firstly, because cystic change in the pancreas commonly conceals a carcinoma. Grossly, such cystic change may look benign, and biopsy specimens for frozen section may not include the malignant area. At the time of operation, therefore, it is a wise precaution to treat a suspected benign cystadenoma as a resectable carcinoma.

Secondly, malignant pancreatic cystadenomas are thought to arise from preexisting benign cystadenoma, especially if the lining epithelium is of tall columnar cells resembling pancreatic duct epithelium or intestinal epithelium.[2] Thus, anything less than total excision will leave behind potentially malignant tissue.

Finally, benign cystadenomas of the pancreas have reportedly reached considerable size—25 cm. or so in diameter.[3] Unless the surgeon attempts total excision, relentless growth of the remaining tumour may eventually cause further symptoms due to pressure on adjacent structures.

In our patient, the size and position of the tumour made pancreaticoduodenectomy the procedure of choice. This rather radical procedure for a benign lesion is justified by the three reasons listed above. At operation we were mainly concerned that the cystic change was secondary to a carcinoma.

The operation was technically simple, the adjacent tissues were in good condition and the patient was not debilitated by her tumour. This appears to be in contrast with patients with a pancreatic carcinoma in a similar site. Hence, one can anticipate a good postoperative course and a good overall result in patients with benign cystadenoma of the pancreas, especially if the tumour is small.

Summary

Benign cystadenoma, a rare tumour of the pancreas, gives rise to non-specific symptoms associated with pressure of the enlarging tumour on contiguous structures. Because most of these tumours affect the body and/or tail of the pancreas, jaundice is an uncommon presenting symptom.

The tumour should be totally excised for three reasons: (1) it is grossly indistinguishable from cystic change associated with a carcinoma, (2) it may be potentially malignant and (3) the tumour may grow to a considerable size and further impinge on adjacent structures.

A 60-year-old woman with a benign multiloculated cystadenoma of the head of the pancreas presented initially with obstructive jaundice which later resolved. She was subsequently shown to have partial obstruction of the lower end of the common bile duct. Total excision of her tumour was successfully achieved by pancreaticoduodenectomy.

The authors wish to thank Dr. D. E. Ryder, Department of Pathology, and Miss Ann Murray, Department of Photography, for their kind assistance.

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Résumé

L'adénome kystique bénin du pancréas, tumeur rare, s'observe plus fréquemment chez la femme et au cours des cinquième et sixième décennies de la vie. La forme papillaire est plus fréquente que la forme multiloculaire. Ses symptômes ne sont pas spécifiques et correspondent à la pression

exercée par la tumeur en voie de développement sur les structures anatomiques contiguës. Etant donné que la majorité de ces tumeurs siègent dans le corps et la queue du pancréas (ou l'une des deux régions), l'ictère est un symptôme peu fréquent. Elles ne sont généralement diagnostiquées qu'au moment de l'opération, surtout si la tumeur est de petite taille.

Il importe de pratiquer une excision radicale et ce pour trois raisons: (1) macroscopiquement, la tumeur ne peut être distinguée des modifications de nature kystique accompagnant un carcinome; (2) la dégénérescence maligne est possible et (3) elle peut atteindre des dimensions considérables et comprimer davantage les structures adjacentes.

Au Women's College Hospital de Toronto, Ontario, nous avons vu pour la première fois un adénome kystique multiloculaire bénin chez une femme qui présentait en même temps une jaunisse d'origine cholostatique. L'ictère a disparu sans traitement spécifique, mais on a découvert subséquemment qu'elle avait une occlusion partielle de l'extrémité inférieure du cholédoque. Au moment d'opérer, on décida d'exciser radicalement la lésion kystique au moyen d'une pancréatico-duodénectomie, de crainte qu'elle ne fût associée à un carcinome.

RENAL VEIN RENIN ACTIVITY IN RENOVASCULAR HYPERTENSION

Surgical correction of hypertension secondary to renal artery disease depends on arteriographic determinations of renal artery disease and specific functional diagnostic methods. The intravenous pyelogram provides a useful screening test, and the divided kidney function tests provide useful functional information related to unilateral or asymmetric renal ischemia, but neither test provides dependable prognostic value.

A measurement of renin activity might also be significant in the evaluation of patients with suspected renovascular hypertension. To determine the value of renin activity, 25 patients with renovascular hypertension were studied. In all instances, rapid-sequence intravenous pyelograms were obtained. Complete criteria for positive study included a 1.5-cm. or more difference in renal size, disparity in early nephrogram effect, disparity in pyelocalyceal appearance time, and a high concentration of contrast media in the suspected kidney. Secondly, divided kidney function tests were made on 19 of the 25 patients. Collections for determination of respective urine flow rates, urinary concentrations of para-aminohippuric acid, creatinine, and sodium, and separate renal clearances of para-aminohippuric acid and creatinine were obtained on all patients.

Blood for renin activity assay was drawn from the right and left renal veins and from the inferior vena cava. Patients were on a normal salt intake without premedication and were recumbent for three hours before renal vein sampling. On two patients, studies were done in both recumbent and tilted positions. Values were also obtained for renin activity from peripheral plasma of six normotensive patients.

Seventeen women and eight men between 16 and 57 years of age who had hypertension for an average of 2.5 years were surgically treated. Mural dysplasia was found in 20 renal vascular lesions, and atherosclerotic lesions in four. One patient, treated by nephrectomy, had a hypoplastic kidney without specific arterial disease. Eighteen patients had arteriographic evidence of renal artery lesion, five bilateral. The length of follow-up studies ranged from six months to three years, and patients were considered cured if the blood pressure was 140/90 mm. Hg or less without drugs six months or longer after operation. Improved patients showed a reduction in diastolic pressure of 15 mm. Hg or more or were normotensive after treatment that previously was ineffective. Both pressure gradients and electromagnetic flowmeter studies were performed.

Of the 25 patients, six had nephrectomy, one a secondary nephrectomy, and one a part of a one-stage bilateral procedure. Twenty angioplastic procedures were done in 19 patients.

Intravenous pyelograms were abnormal in 89% of the patients with unilateral renal artery disease, at least one of the split function tests was positive in 10 of 12 patients cured by operation and in three of four improved by operation. Absolute values of plasma renin activity had doubtful diagnostic significance, but a ratio of 1:5 indicated functionally significant renal artery stenosis irrespective of absolute values. The study did not prove that assay of renal vein renin activity can totally replace divided kidney function tests. Rather, the methods apparently complement each other.—Kaufman JJ, Lupu AN, Franklin S, et al: Diagnostic and predicative value of renal vein renin activity in renovascular hypertension. *J Urol* 103: 702, 1970

SPINAL CORD COMPRESSION IN POLYOSTOTIC FIBROUS DYSPLASIA*

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In fibrous dysplasia, normal bone which undergoes physiologic lysis is replaced by abnormal fibrous tissue proliferation.[1] Mono-ostotic and polyostotic varieties have been described. The polyostotic type may be associated with cutaneous pigmentation and sexual precocity in females—a condition termed Albright's syndrome.[2]

Vertebral involvement is rare in polyostotic fibrous dysplasia; Harris, Dudley and Barry[3] reported an incidence of 14%. Spinal cord compression in polyostotic fibrous dysplasia affecting the vertebrae is even rarer. So far, only nine such cases have been reported in the literature.[4-7]

This paper describes a patient with polyostotic fibrous dysplasia who presented with paraplegia.

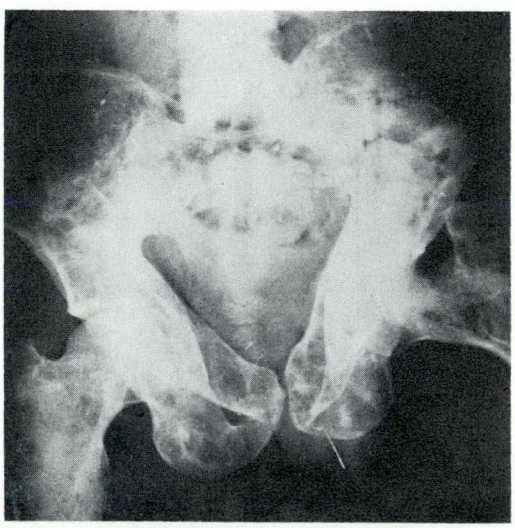

Fig. 1.—Radiograph of the pelvis showing multiple osteolytic areas in the pelvis and upper part of the femur. Distortion of the pelvis is also evident.

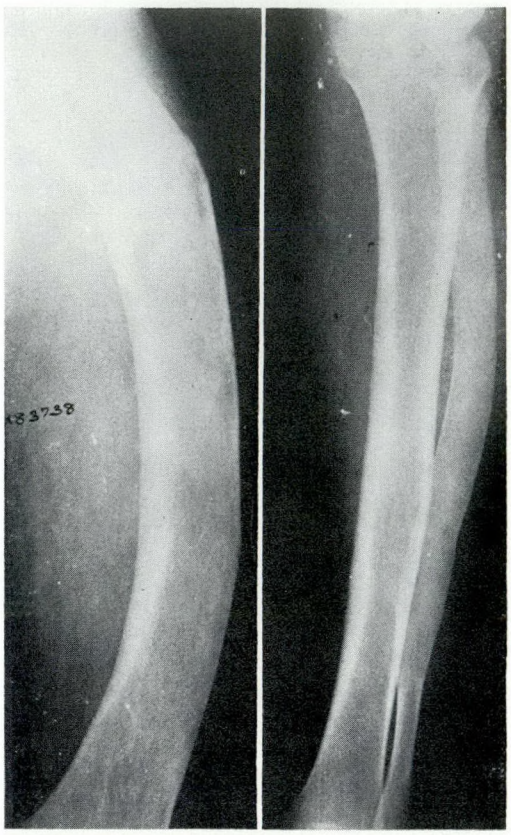

Fig. 2.—Femur and leg bones showing "shepherd's crook" deformity of the femur and the irregular appearance of the shaft of the fibula.

Case Report

A 20-year-old man was admitted to the neurological service of the Christian Medical College Hospital, Vellore, on September 4, 1969, complaining of the sudden onset of paralysis of both lower limbs associated with moderate pain in the dorsal spine. He also had urinary retention with dribbling. From the age of 10 years his lower extremities were deformed, and the left lower limb was three inches shorter than the right. He walked with a limp, but had never consulted a doctor for this reason. He was working as a mechanic in a garage. There was no family history of similar complaints.

On examination, the patient was dwarfed and greatly deformed. He had frontal bossing of the skull, dorsal kyphosis with slight scolio-

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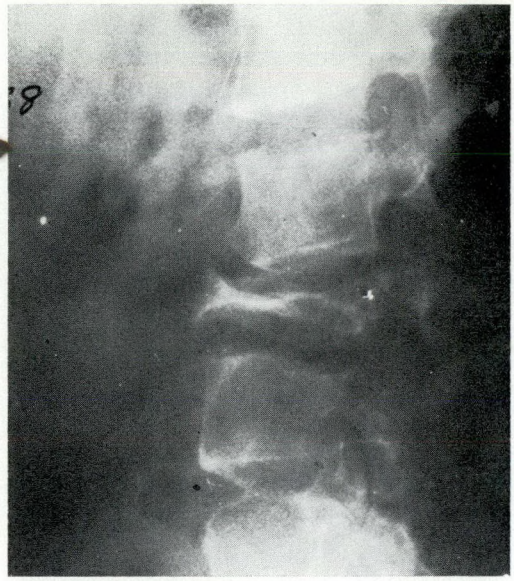

Fig. 3.—Lumbar spine showing collapse of the L3 vertebra.

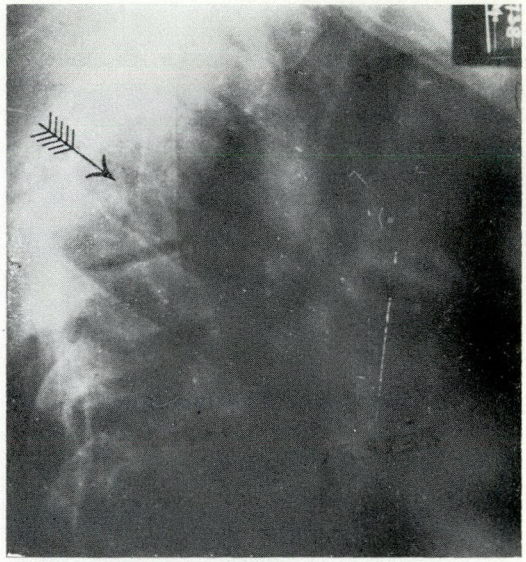

Fig. 4.—Thoraco-lumbar spine showing pathologic fracture dislocation between T5 and T6 (arrow).

sis, exaggerated lumbar lordosis, pigeon chest deformity, prominent Harrison's sulcus, "shepherd's crook" deformity of the left thigh and bowing of both legs. There was no abnormal cutaneous pigmentation and there were no endocrine abnormalities. Neurologic examination revealed paraplegia with a sensory level at the T6 dermatome. Motor power was grade 0 (MRC scale) in the lower limbs. Deep-tendon reflexes in the lower limbs were exaggerated. Superficial reflexes were lost, and he had bilateral Babinski responses. Upper limbs and cranial nerves were normal.

On radiographic examination he had multiple bony lesions compatible with polyostotic fibrous dysplasia (Figs. 1-3). Angulation was evident between T5 and T6 in the film of the dorsal spine (Fig. 4). He had a normal leukocyte count and hematocrit. Cerebrospinal fluid was clear, with a normal cell count, 260 mg./100 ml. protein and 80 mg./100 ml. glucose. Manometry revealed a partial block at T4. Serum calcium was 10.5 mg./100 ml. and serum phosphate was 3.4 mg./100 ml. Urinary calcium excretion was 86 mg./24 hrs. and urinary phosphorus excretion was 342 mg./24 hrs. (These are within the normal range in our laboratory.) Alkaline phosphatase was 26 King-Armstrong units. He had a total serum protein of 7.9 g./100 ml., albumin of 5.3 g./100 ml. and globulin of 2.6 g./100 ml. Serum electrophoresis showed normal proportions of the various proteins. Lumbar myelography confirmed the partial block at the T4 level.

At biopsy, bone was obtained from the left femur. Histologic sections showed spindle cells arranged loosely with many small blood vessels, and thin bony trabeculae, forming arches or segments of circles in it (Fig. 5). Osteoblasts lined these arches of osteoid trabeculae and there were occasional osteoclastic giant cells in the stroma. Bone from the adjacent areas showed normal structure.

The spinal cord was decompressed by laminectomy from T3 to T6. It was severely stretched over the angulation of the spine. There was no abnormal tissue in the extradural space which could have compressed the spinal cord. After operation the spasticity and motor power improved (the latter to grade 3), but the reflexes remained unaltered.

Discussion

Conditions that produce multiple bone lesions similar to polyostotic fibrous dysplasia are hyperparathyroidism, Hand-Schüller-Christian disease, Paget's disease of bone, and generalized neurofibromatosis. The normal biochemical findings in this patient and the normal pattern of the unaffected areas of the skeleton rule out hyperparathyroidism and Paget's disease. The clinical features and histopathology also help to exclude Paget's disease and Hand-Schüller-Christian disease. Generalized neurofibromatosis is invariably associated with cutaneous pigmentation or

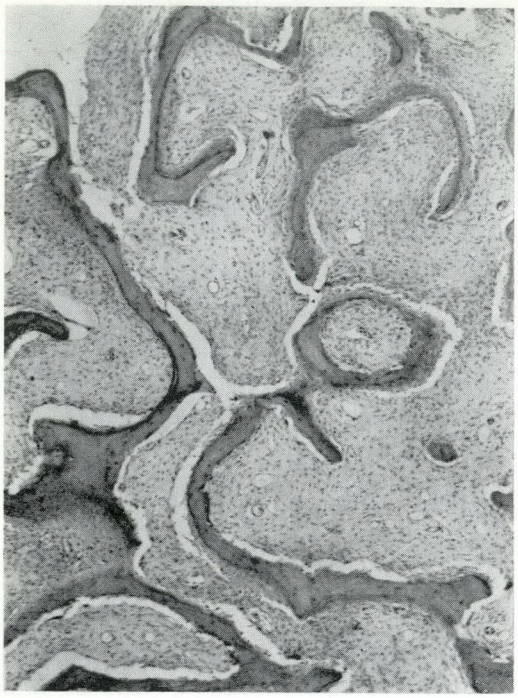

Fig. 5.—Microscopic appearance of the biopsy specimen from the femur (H & E × 120).

hypertrophy of the tissues, which this patient did not have. The histologic findings of the loose fibrous stroma and thin trabeculae of bone, with the characteristic pattern in the biopsy, confirm the diagnosis of polyostotic fibrous dysplasia.

The spinal cord involvement in the present case was secondary to a pathologic fracture of the vertebrae, unlike the case reported by Montoya, Evarts and Dohn.[7] These authors found a large mass of soft gritty tissue in the epidural space causing compression of the spinal cord; their patient improved remarkably after the operation.

Because very few patients with polyostotic fibrous dysplasia and spinal cord compression have been treated by operation it is difficult to decide on the best form of surgical management. All those reported in the literature were treated by laminectomy and all were reported to have done well as indicated by postoperative neurologic status, as did our patient. Until we have more experience and have determined the results of other surgical measures, such as anterolateral decompression or transthoracic anterior decompression, laminectomy and spinal cord decompression seem to offer the best approach to the problem.

Summary

A 20-year-old man was admitted to hospital because of the sudden onset of paraparesis. He had multiple bony deformities and a gibbus deformity of the dorsal spine. Radiographs revealed changes suggestive of polyostotic fibrous dysplasia, and biochemical studies and bone biopsy supported the diagnosis. Paraplegia was due to spinal cord compression by collapsed and angulated dorsal vertebrae. Laminectomy and decompression of the spinal canal resulted in moderate recovery of function below the lesion.

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Résumé

Un jeune homme de 20 ans a été hospitalisé au Christian Medical College Hospital de Vellore (Indes), pour un début brusque de paraparésie. Il présentait de nombreuses difformités osseuses et une gibbosité de la colonne dorsale. Des radiographies ont révélé des modifications osseuses laissant présager une dysplasie fibreuse des os. Des analyses biochimiques et une biopsie osseuse ont confirmé ce diagnostic. La paraplégie relevait d'une compression médullaire causée par un affaissement vertébral et une angulation anormale des vertèbres. Une laminectomie et la décompression du canal rachidien ont donné une certaine amélioration fonctionnelle en dessous de la lésion.

ANTERIOR TIBIAL COMPARTMENT SYNDROME COMPLICATING FEMORAL EMBOLECTOMY

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GITLITZ[1] described the anterior tibial compartment syndrome as ischemic necrosis with variable functional impairment of the neuromuscular contents of that discrete fascial space known as the anterior tibial compartment. Sufficient cases have been reported to emphasize that a number of etiologic factors may be involved. Several have been described after arterial embolism,[2, 3] but the syndrome has not previously been reported as a complication of femoral embolectomy. This paper describes two patients who suffered this complication after an otherwise successful embolectomy.

CASE REPORTS

Case 1.—A 60-year-old New Zealand woman was admitted to the University College Hospital, London on May 15, 1968, three days after the onset of severe pain in the right calf and foot. She had a five-year history of atrial fibrillation and a two-year history of bilateral calf claudication after walking 50 yards. In 1966 she had a mild attack of congestive cardiac failure for which she was treated with digitalis, Inderal (propranolol HCl) and diuretics. She also had polycythemia which had not been treated.

This slim plethoric woman had widespread rosacea. Her blood pressure was 150/90 mm. Hg. Left ventricular hypertrophy was present but there were no signs of congestive cardiac failure. Both femoral pulses were palpable but there was no pulsation distal to these. Below the knee both legs were cold and the veins empty. There was anesthesia from half-way down the right shin, and the skin was dusky blue. The left foot was also discoloured but there was no sensory loss.

Her hemoglobin was 148% (21.6 g./100 ml.), hematocrit 65%, leukocyte count 11,400/c.mm. with a normal differential count. Platelets were normal, sedimentation rate was 38 mm. in one hour (Westergren). The blood urea nitrogen was 56 mg./100 ml. Her electrocardiogram showed atrial fibrillation with ischemic changes.

We made a diagnosis of right superficial femoral artery thrombosis secondary to atherosclerosis and polycythemia.

An intravenous infusion was set up and 500 ml. of low molecular weight dextran (Rheomacrodex) was given over four hours. Heparin, 100 mg. every six hours, was given intravenously by the same route. We attempted to reduce the polycythemia by withdrawing 800 ml. of blood and replacing it with reconstituted plasma. With this treatment, the condition of the left foot improved considerably but because the right foot had deteriorated, we explored the right femoral artery.

After the bifurcation of the right femoral artery was exposed and a transverse arteri-

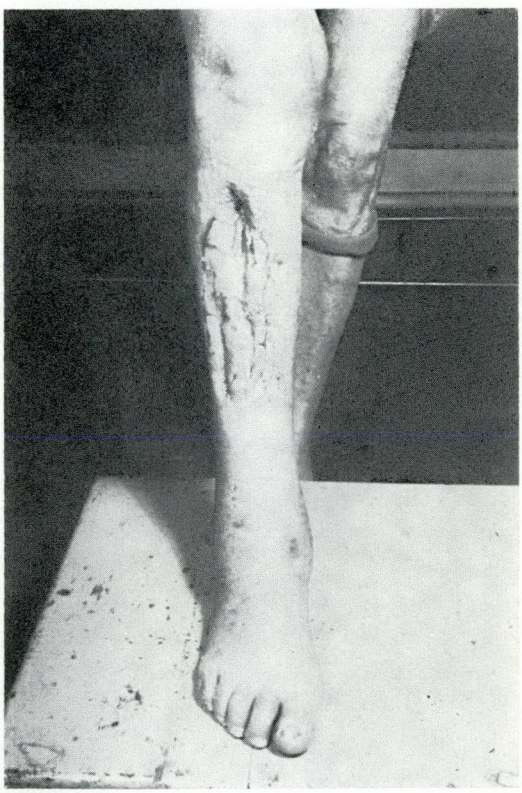

Fig. 1.—Case 1. The anterior tibial compartment after application of patch grafts.

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otomy made, we discovered that an embolus had lodged at the bifurcation of the femoral artery; there was little propagated thrombus and the vessels were otherwise normal. Using a Fogarty catheter, the superficial and deep femoral arteries were cleared of clot. The arteriotomy was sutured with 5-0 continuous silk.

After operation the right femoral, popliteal and posterior tibial pulses had good volume. The dorsalis pedis pulse was absent throughout the patient's convalescence. Two days later, when she complained of pain in the region of the right shin, we found that the skin was discoloured over the right anterior tibial compartment and that she had developed a foot-drop. She had paresthesia in the foot and sensory loss in the first toe cleft. The condition of the skin over the anterior tibial compartment deteriorated over the next two weeks and eventually sloughed together with much of the underlying muscle. Culture from the slough grew *Proteus mirabilis* and *Staphylococcus pyogenes*. The dead tissue was later excised and patch grafts were applied (Fig. 1). She was discharged after three months with a dorsiflexion caliper for the correction of the foot-drop.

Case 2.—A 54-year-old general practitioner was admitted to the University College Hospital, London on June 20, 1968, suffering from severe gastroenteritis. He was otherwise well although he had recently developed claudication in the right calf during long walks. On admission he required intravenous fluid replacement. Two hours after admission he suffered a myocardial infarction and two hours later developed sudden severe pain in his left leg. At this time his blood pressure was 130/80 mm. Hg. He had a bounding left femoral pulse but no pulses were palpable distally. The left leg was white and cold, the veins were collapsed and there was no sensation over the dorsum of the foot and toes. We made a diagnosis of left femoral embolism secondary to a cardiac mural thrombus and treated him with 100 mg. heparin intravenously, 500 ml. of Rheomacrodex and 500 ml. of plasma. Four hours elapsed before he was considered fit enough for embolectomy.

After the left common femoral artery was exposed, the superficial and deep femoral arteries were cleared of clot through a transverse arteriotomy using a Fogarty catheter. The arteriotomy was closed with continuous 5-0 silk suture and the patient sent back to the ward. The wound continued to ooze blood and the patient was returned to the operating room five hours later for resuture of the arteriotomy. The popliteal and posterior tibial pulses were present throughout, but the dorsalis pedis pulse did not return until the third postoperative day. During this period the patient complained of severe pain in the anterolateral aspect of his left lower leg, which was increased by the slightest touch. He had a left foot-drop with an area of anesthesia in the first toe cleft. The skin over the anterior tibial compartment was edematous and bluish. The skin did not deteriorate and no grafting or other treatment was required. When he was discharged from hospital a month later, the skin was healthy, but the anterior tibial compartment was still tender to palpation. The sensory loss was constant with an area of hyperesthesia around it. He required a dorsiflexion caliper to correct the foot-drop.

Discussion

The anterior tibial compartment syndrome was first described by Sirbu, Murphy and White in 1944[4] as a complication of the repair of a small muscle hernia through the anterior crural fascia. However, in 1943, Vogt described the syndrome in a soldier after prolonged marching[5] and it has subsequently been observed repeatedly in individuals, usually young, who have been subjected to unaccustomed strenuous exercise.[6] It has also been reported after local trauma, sometimes as minor as a twisted ankle, but often after more major accidents.[7] Carter described this misadventure after blood transfusion into the vein of a foot in which the blood presumably tracked up a synovial sheath. It has been reported as a complication of atherosclerosis obliterans and diabetes mellitus,[7] of proximal arterial thrombosis[8] and femoropopliteal bypass.[1] The literature contains two references to this syndrome after arterial embolism[2, 3] which was treated conservatively by various methods such as oral Priscoline (tolazoline HCl), intra-arterial papaverine sulfate and paravertebral lumbar sympathetic block. Embolectomy was not done in these two instances.

Anatomy

The anterior tibial compartment is bounded anteriorly by the deep fascia,

medially by the crest and lateral surface of the tibia, posteriorly by the interosseous membrane and laterally by the fibula and anterior intermuscular septum. It contains the tibialis anterior, extensor digitorum longus, extensor hallucis longus and peroneus tertius muscles. Some workers have suggested that this is an inexpansile compartment, *viz.* that the tendons plug the inferior aspect of the compartment as they pass under the superior extensor retinaculum.

The anterior tibial nerve, the main branch of the lateral popliteal nerve, is given off as that nerve winds round the lateral aspect of the neck of the fibula. It enters the compartment by piercing the anterior intermuscular septum. This nerve provides the motor supply to the muscles in the compartment and the extensor digitorum brevis on the dorsum of the foot. Its sensory branch supplies only the area of the first toe cleft.

The anterior tibial artery enters the compartment through a defect above the interosseous membrane and runs distally to leave inferiorly as the dorsalis pedis artery. This artery supplies the muscles of the compartment but the 12 to 16 branches to the tibialis anterior muscle are virtually end-arteries.[9] The other muscles have an alternative anastomotic supply either from the peroneal or posterior tibial arteries.

In this syndrome the onset of pain in the anterolateral aspect of the leg is followed, 12 to 24 hours later, by swollen, tense, brawny induration of the skin over the anterior tibial compartment. The muscles in the compartment are tender to palpation and there is usually a weakness of dorsiflexion. There may be loss of the dorsalis pedis pulse and sensory loss in the first toe cleft.[1] Putty-like material may be discharged and, if the space is explored,[10] this can be seen to originate mostly from the necrotic tibialis anterior muscle.

On microscopy the spectrum of changes ranges from coagulative necrosis with loss of striation and of nuclei, to complete loss of architecture with infiltration by inflammatory cells. Later the necrotic muscle is replaced by fibrous connective tissue which may contain scattered islands of muscle.[1]

Anterior Tibial Nerve and Foot-Drop

Previously the foot-drop was believed to be neurologic. Carter, Richards and Zachary[6] disproved this and showed that the drop was due chiefly to muscle necrosis. They admitted that the nerve was affected to a varying extent by local ischemia or increased pressure within the space but pointed out that the foot-drop does not recover when sensation returns. The foot-drop may improve somewhat when the fibrous scar tissue contracts.

Because muscle necrosis, caused by a rise in pressure in the compartment, and atrophy of the muscle, caused by nerve injury in the absence of muscle necrosis, have not always been distinguished in the literature we should emphasize here that the two clinical methods for testing for nerve involvement or regeneration, *viz.* stimulation of the extensor digitorum brevis on the dorsum of the foot and sensory testing in the first cleft, are themselves open to criticism. In the first method, the muscle is also supplied by the dorsalis pedis artery and its arterial supply may be compromised if this pulse is absent. In the second, surgical division of the anterior tibial nerve does not always produce sensory loss in the first toe cleft; therefore the absence of apparent anterior tibial nerve involvement does not necessarily mean that the foot-drop is produced as a result of nerve necrosis.

Pathogenesis

Hughes[11] believed that this syndrome was primarily vascular and pointed out that if increased compartmental tension alone was the cause, all the muscles would be affected equally. In contrast to the other muscles in the compartment, the branches of the anterior tibial artery that run to the tibialis anterior muscle are virtually end-arteries; this may explain this muscle's increased vulnerability.

Muscle swelling in an inexpansile compartment probably produces occlusion of the local capillaries, venules and lymphatics. This occlusion leads to extravasation of fluid and raises still further the pressure in the anterior tibial compartment, to a point where even the arterial supply is

prejudiced and the dorsalis pedis pulse eventually becomes impalpable. All the precipitating factors so far described could operate on this basis. After thrombosis, embolism, surgical or other trauma to the femoral or popliteal artery, sufficient blood must enter the limb to avoid gangrene of the foot. This relative ischemia produces swelling of all the distal muscles of the limb but only in the inexpansile compartment, which contains the dorsiflexors of the foot, does the vicious circle produce muscle necrosis. Severe unaccustomed exercise produces generalized muscle swelling in the limb but only in the inexpansile anterior tibial compartment is this occasionally disastrous.

The remaining etiologic factors—repair of muscle hernias through the anterior crural fascia, hematoma from muscle rupture after direct trauma such as a twisted ankle, and blood tracking up a synovial sheath after faulty blood transfusion—can be explained on the same principle, that is, on increase of volume within an inexpansible compartment.

After embolectomy this syndrome can be prevented by one of two measures: (1) Ensure that the anterior tibial artery is cleared of clot or propagated thrombus. If there is any doubt, do arteriography to make sure. (2) Perform an anterior crural fasciotomy as a prophylactic measure if the dorsalis pedis pulse is not palpable after the embolus is removed.

Summary

Two patients developed the anterior tibial compartment syndrome after otherwise successful embolectomy—a misadventure not previously reported.

This syndrome is probably caused by swelling of the tibialis anterior muscle after a period of arterial occlusion. Swelling of the muscle in the inexpansile anterior tibial compartment leads to occlusion of veins, lymphatics and finally arteries, producing nerve death as well as muscle necrosis. To prevent this syndrome, subcutaneous crural fasciotomy should be considered if, after embolectomy, the dorsalis pulse cannot be palpated.

The photograph of Case 1 is reproduced by the kind permission of Mr. D. N. Matthews.

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Résumé

Après avoir subi une embolectomie, par ailleurs parfaitement réussie, deux opérés ont présenté le syndrome de la loge tibiale antérieure. Cette complication n'avait pas été signalée jusqu'à présent.

Ce syndrome est probablement causé par l'enflure du muscle jambier antérieur après une certaine période d'occlusion artérielle. L'enflure du muscle dans la loge du tibia antérieur, qui est inexpansible, aboutit à l'occlusion de veines, de vaisseaux lymphatiques, puis d'artères, et finalement à la mort du nerf et à la nécrose musculaire. Pour prévenir cet accident, on peut envisager de pratiquer une fasciatomie crurale par voie souscutanée si, après embolectomie, l'artère pédieuse ne peut être palpée.

FRACTURE DISLOCATION OF THE UPPER HUMERUS INTO THE THORACIC CAVITY*

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THREE patients have been described who sustained severe fracture dislocation of the upper humerus into the thoracic cavity,[1-3] none of which required thoracotomy. In the woman described in this paper, thoracotomy was a life-saving procedure, and her case presented three interesting aspects: first, such fracture dislocation is an unusual cause of severe traumatic hemopneumothorax. Second, the findings at early exploration suggested a new mechanism of injury that allows the humeral head to remain separated and free in the thoracic cavity. Third, this potentially lethal injury occurred in an elderly woman after minimal trauma.

CASE REPORT

The patient, an obese 73-year-old woman, was admitted to the Emergency Department of Sunnybrook Hospital, Toronto, apprehensive and uncooperative. Her chief complaint was of left shoulder pain. Earlier she had fallen down three steps onto her outstretched right arm, then a further three steps to the ground, landing on her outstretched left arm.

She was in shock and had a pulse rate of 120/min. and a systolic blood pressure of 80 mm. Hg. She was not in respiratory distress, but had surgical emphysema over the anterior left upper chest. There were no palpable rib fractures. There was increased resonance to percussion over the left upper chest, and the breath sounds were diminished. Left arm and shoulder movements were painful; clinically, we thought the left humeral neck was fractured. There were no abnormal neurologic findings in the left upper limb, the extremity was warm and the peripheral pulses were present. The right wrist had the "dinner-fork" deformity of a Colles' fracture.

Full physical examination was otherwise normal and there was no obvious cause for the patient's hypotension. A rapid infusion of 500 ml. Ringer's lactate solution restored the systolic blood pressure to 140 mm. Hg. Needle aspiration revealed a pneumothorax and a chest tube was inserted through the second interspace in the mid-clavicular line. Underwater seal drainage produced air and blood. At this point, the patient's condition appeared to be stable.

Laboratory investigations produced the following results: hemoglobin, 12 g./100 ml.; blood urea nitrogen, 15 mg./100 ml.; serum sodium, 135 mEq./l.; potassium, 3.6 mEq./l.; chloride, 101 mEq./l., carbon dioxide combining power, 20 mEq./l.; blood sugar, 81 mg./100 ml.; and electrocardiogram normal.

A posteroanterior chest film (Fig. 1) demonstrated a severe fracture of the neck of the

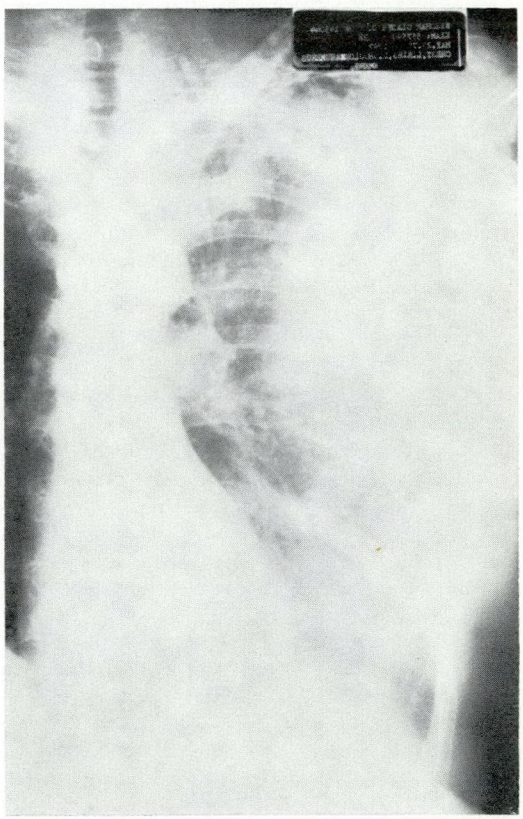

Fig. 1.—Posteroanterior radiograph demonstrating pleural effusion, fracture of the neck of the humerus with the head apparently in the thoracic cavity, fractures of the second, third and fourth ribs, and a fracture of the glenoid (note that the chest tube has become displaced).

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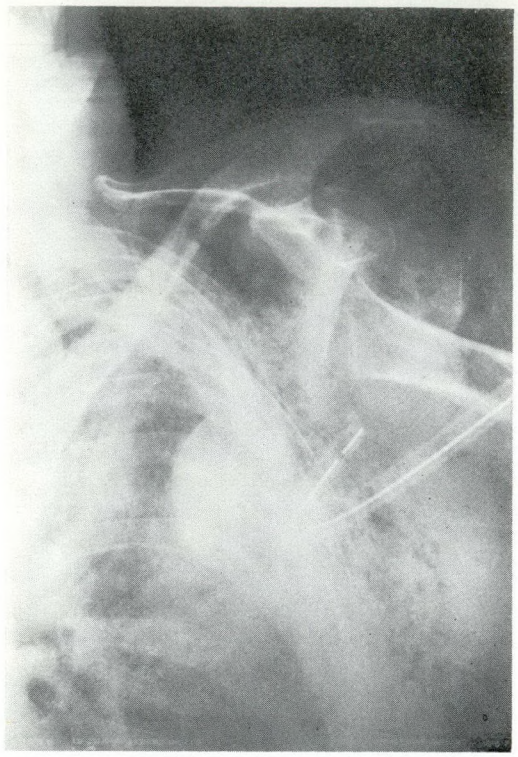

Fig. 2.—Stereoscopic view of the left shoulder joint. The head of the humerus is lying in the thoracic cavity.

humerus, a fracture of the glenoid and a "flail" segment of second, third and fourth ribs anterolaterally. There was a left pleural effusion. Stereoscopic views (Fig. 2) showed the humeral head in the left thoracic cavity.

During this examination the patient again became hypotensive and did not respond to infusions of whole blood. The chest drain had become displaced, so a new drain was inserted and the patient prepared for emergency thoracotomy.

A standard left thoracotomy was made through the bed of the fifth rib. There was a massive hemothorax, the source of which was not immediately evident, and the patient remained hypotensive. The free humeral head was immediately identified and removed from the cavity. The apex of the thoracic cavity was then packed off to allow resuscitation by continued whole-blood replacement.

When the patient's blood pressure had stabilized, removal of the packing revealed an 8-cm. long laceration in the apical lateral aspect of the left upper lobe. There were no adhesions of the lung to the chest wall. The laceration was 5 cm. deep, was not bleeding, but leaked a small amount of air. The adjacent segment of chest was unstable over an area 12 cm. long in the region associated with double fractures of the second, third and fourth ribs. The third intercostal space was extensively lacerated at what we presumed to be the site of penetration by the upper humerus. Bleeding did not resume after the packing was removed. The original source of the bleeding appeared to be the intercostal vessels. The vessels of the second to fifth interspaces were ligated with heavy silk, and the lung laceration was closed with a running chromic catgut suture, after we had inflated the lung to be sure that there was no major bronchial communication. Two chest drains were attached to an Emerson pump and the wound was closed.

For the first 24 hours the patient was managed with an Emerson volume ventilator and an endotracheal tube. Because we could not "wean" the patient from the ventilator at this time, a tracheostomy was performed, and assisted ventilation continued for a further five days. The tracheostomy tube was removed on the fifteenth postoperative day.

Because the patient was critically ill at the time of operation, the shoulder injury was managed conservatively. We did not replace the humeral head with a prosthesis during this operation.

The patient had no residual chest complaints four months after her injury. She had not regained active glenohumeral abduction but could carry on limited domestic activity. We contemplate no further operation.

Discussion

This patient's mode of presentation emphasizes that concealed intrathoracic hemorrhage may precipitate profound hypovolemic shock without signs of severe chest injury. We believe that the major source of bleeding was the intercostal vessels in the "flail-chest" segment and that the lung laceration, a limited injury, contributed little to the patient's shock.

Severe fracture dislocation of the upper humerus with extracapsular displacement of the head fragment, a rare lesion, accounts for 1.1%[4] and 1%[5] of reported shoulder fractures and dislocations. Most fracture dislocations are anterior and occur in obese elderly women. Displacement of the separated humeral head into the thoracic cavity has been described three times previously.[1-3]

Authors of previous papers, describing this injury, believed that the humeral neck fractured as it lay between the ribs following dislocation. For the following reasons we propose that the fracture *precedes* the dislocation.

The pattern of fracture is constant whether the head comes to lie finally in the chest or, more commonly, in the axilla.[4, 6] This fracture can be reproduced consistently by applying a longitudinal force[7] such as would be applied during a fall onto the outstretched hand with the humeral head still within its socket, but not by angulatory forces to the humeral neck as would occur if dislocation preceded fracture.[5]

If the subject falls on the abducted outstretched arm, the dislocated upper humerus would then be directed against or, rarely, into the chest. Manipulation during transportation, muscle recoil, or gravity could cause the shaft to return from the chest, leaving the head trapped in the thorax.

Severe axillary vessel damage is rare in fracture dislocation of the humerus because the sharp upper-humeral shaft is still capped by the head when it traverses the axilla. The lung laceration in this patient could have been caused by sudden blunt trauma to a fully inflated lung, although this damage to the lung may have been inflicted by the sharp uncovered proximal humeral shaft after displacement of the head (Fig. 3).

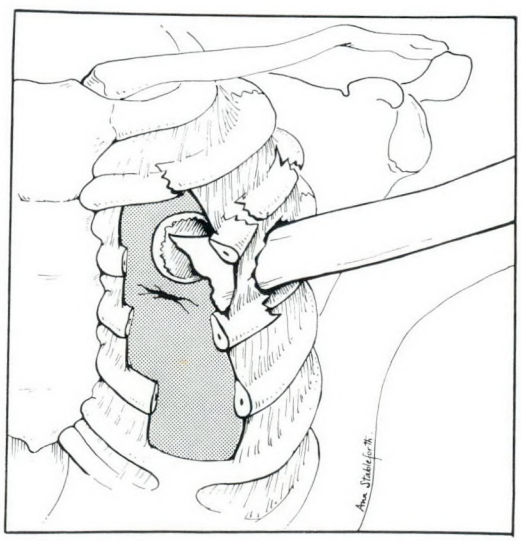

Fig. 3.—Artist's impression of the mechanism of thoracic injury.

Summary

An elderly woman sustained a severe fracture dislocation of the left upper humerus into the thorax during a fall. The free head of the humerus remained in the thoracic cavity while the shaft returned to its normal anatomic position.

The patient presented in shock, which failed to respond to conservative treatment and necessitated emergency thoracotomy. A deep laceration of the left upper lobe was found; however, the massive hemothorax originated from torn intercostal vessels of a "flail" segment involving the second to fourth ribs. This finding emphasizes that occult intrathoracic bleeding may cause severe hypovolemic shock after relatively minor trauma.

Previous authors describing this injury believed that the humeral head, following dislocation, fractured as it lay between the ribs. We propose a different mechanism of injury, *viz.* that the fracture precedes the dislocation and when the capped humerus comes to lie in the thoracic cavity the head can separate. The shaft then returns to its anatomic position leaving the free head in the thoracic cavity.

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Résumé

Après une chute, une femme âgée a subi une fracture-luxation de l'humérus supérieur gauche qui a pénetré dans la cavité thoracique. La tête libre de l'humérus resta dans la cavité thoracique, tandis que la diaphyse de l'humérus revenait à sa position anatomique normale.

L'état de choc de la blessée ne cédant pas au traitement conservateur classique, il fallut recourir à la thoracotomie. On trouva une lacération profonde du lobe supérieur, mais l'hémothorax massif provenait de vaisseaux intercostaux lacérés dans un "volet" thoracique qui affectait les côtes, de la deuxième à la quatrième. Cette constatation confirme qu'une hémorragie intrathoracique occulte peut provoquer un choc sévère par hypovolhémie et ce, même après un traumatisme relativement mineur.

D'autres auteurs en décrivant cette lésion estimaient que la tête de l'humérus après luxation s'est fracturée alors qu'elle reposait entre les côtes. Personnellement, nous croyons à un mécanisme différent: la fracture précède la luxation et quand l'humérus est emprisonné dans la cavité thoracique, la tête peut se séparer. La diaphyse revient alors à sa position anatomique première et la tête de l'humérus demeure dans le thorax.

GIANT CELL TUMOUR

A study of giant cell tumours of the bone was conducted surveying 195 patients between 1910 and 1969. A complete follow-up study was obtained on all but six of these patients. The study revealed that the tumour is more common in female patients less than 20 years of age. Seventy-five per cent of the patients were females. The youngest patient in this series was 12 years old.

Approximately 77% of the giant cell tumours were located at or near the end of a major tubular bone of the extremity. One hundred of the tumours occurred at the knee, 51 at the distal end of the femur, and 43 at the proximal portion of the tibia. In this series, the majority of tumours were observed about the knee joint. The most common complaint of the patient was pain or swelling, or both. Approximately half the patients had symptoms six months before seeking or receiving appropriate medical care.

Grossly, the giant cell tumour is typically grey, brown, or has a mottling of these colours. The tumour is soft and pliable, and grey and white necrotic zones may be present.

In this series, primary treatment consisted of at least 15 different types of management. These included radiation, curettage or excision with or without forms of cautery, with or without bone grafting, and with or without radiation, as well as an *en bloc* resection and amputation. Since the majority of patients had received primary treatment at other institutions before coming to the Mayo Clinic, the primary therapy is difficult to assess. In the treatment of recurrent disease after primary curettage or excision seven patients had amputation and this proved curative. In 11 of the patients with recurrent symptoms after primary treatment with curettage and excision, irradiation without biopsy was given. Five patients were alive and well after seven to 40 years. Five of the remaining six patients had a recurrent giant cell tumour, and after radiation therapy for recurrent tumour developed a sarcoma in the affected region.

Seven patients had complete *en bloc* resections before 1967. Six patients were well for two to 30 years; four of these had been observed for more than 10 years. The seventh patient had a prosthetic replacement of the knee after resection of the primary lesion. Twenty-one patients underwent amputation for benign giant cell tumour in addition to the 10 who had an amputation as primary treatment at the Mayo Clinic.

In this series of patients 17 had malignant giant cell tumours (8.7% of the total). Ten of the 17 patients died of these tumours within one year and one patient died at 3.2 years. One patient survived 55 years after a total resection of the tumour and three patients were long-term survivors after amputation. The authors believe that radiation therapy contributes to the malignant transformation of giant cell tumours.

The shortest interval from radiation to recognition of a post-irradiation sarcoma was 3.7 years. Sarcomas developed in seven of the 37 irradiated patients or 19%. Sarcoma developed in only one of the surgically treated patients (3%). This is an interesting series because of the long-term follow-up study involved.—Dahlin DC, Cupps RE, Johnson EW: Giant-cell tumor; study of 195 cases. *Cancer* 25: 1061, 1970

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Urologische Operationslehre. Number 7. Nierentransplantation. Operative Behandlung des renalen Hochdrucks. Operationen bei Nierenanomalien. Operative Behandlung der Ren mobilis. Edited by G. W. Heise and E. Hienzsch. 120 pp. Illust. VEB Georg Thieme, Leipzig, 1970. DM 35,00. $10.20 (approx.). Paperbound.

Ventriculocisternostomy. Long-Term Experiences. Robert C. Cantu, Jost J. Michelson and James C. White. 138 pp. Illust. Charles C Thomas, Publisher, Springfield, Ill., 1970. $14.75.

(Continued from Adv. p. 26)

operative enterocolitis and foreign bodies in the abdominal cavity.

The chapter on the surgery of the stomach and duodenum by R. Nissen is particularly instructive, dealing in detail with atypical closure of the duodenal stump and with complications after gastrectomy. A surgeon facing postoperative complications or anticipating intraoperative difficulties will profit from a perusal of the appropriate section and will be fascinated by some of the ingenious solutions tried by others.

SURGERY AND BIOLOGY OF WOUND REPAIR. Erle E. Peacock, Jr. and Walton Van Winkle, Jr. 630 pp. Illust. W. B. Saunders Company, Philadelphia; W. B. Saunders Company Canada Limited, Toronto, 1970. $23.25.

We have long needed a book written, in a concise and organized way, with a view to better understanding of the mechanism of repair and regeneration of wounds. The authors have made a commendable contribution in this regard. This is an excellent book, which serves to translate the apparently complex scientific facts of wound repair to practical application in everyday surgery.

The book can actually be divided into two sections. The first, consisting of five chapters, deals with the basics of repair such as inflammation, epithelization, wound contraction, synthesis and maturation of collagen. The second section of the book deals with specific problems and their management. The discussions are based on the principles, beautifully elucidated in the first half.

The facts are presented in a simple and well-organized way, and the style is superb, presenting enjoyable reading. An excellent selection of references is given at the end of each chapter.

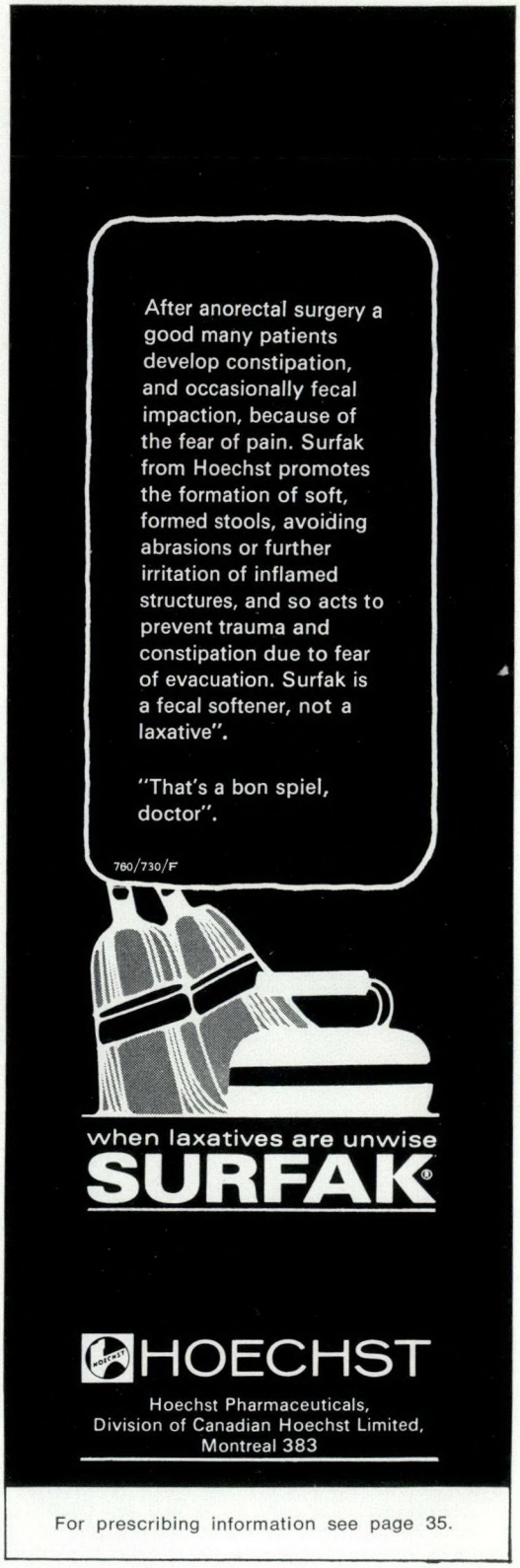
In the section dealing with skin wounds, the author explains why, even though the superficial skin is approximated accurately, a scar sometimes results which is as wide as the wound had been before closure. Here he deals with the desirability of using subcuticular sutures and the necessity for using non-absorbable colourless material.

A special section is devoted to lower leg ulcers popularly, but inaccurately, referred to as "stasis ulcers". The authors' views regarding their treatment are definite and clear. There is a message that many surgeons will find valuable.

The section on burn care and skin grafting is well written. The modern trends in the management of tendon and nerve injuries and their associated problems are given in a logical and understandable way.

The chapter on visceral injuries is rather brief and the section on intestinal anastomoses should have been elaborated further.

On the whole, this excellent book is recommended to all students of surgery.



For prescribing information see page 35.

Less abrasive than a brush ...and just as effective[1]

NOTICE

BRITISH COUNCIL SPECIALIST COURSE

A postgraduate course "Patient Monitoring and Intensive Care" will be held in London, Glasgow and Edinburgh from October 17 to 30, 1971. This course is designed to give clinicians and clinical research workers a theoretical and practical survey of the rapidly developing field of patient monitoring and intensive care. The course will be directed by Professor J. P. Shillingford of the Medical Research Council Cardiovascular Research Unit, Royal Postgraduate Medical School, London. The course has been planned to cover instrumentation, patient management and nursing care as well as the organization of intensive care units in coronary, renal, respiratory, neurologic and other diseases, and intensive postoperative care.

The provisional program is as follows.

London—Royal Postgraduate Medical School (J. P. Shillingford and colleagues)—Monitoring in anesthetics; instrumentation and organization for research into, and treatment of, myocardial infarction; the intensive care of the acute respiratory emergency; treatment and instrumentation used in the management of respiratory failure; and renal dialysis. Medical Research Council Division of Medical Engineering (H. Wolff and colleagues)—New methods of advanced instrumentation in monitoring and patient care. St. Thomas's Hospital (G. Spencer)—General intensive care in a teaching hospital.

Glasgow (two days)—Western Infirmary and other hospitals (T. D. V. Lawrie and colleagues)—Hyperbaric oxygen; renal intensive care; neurosurgical intensive care; general postoperative intensive care; intensive care of the respiratory patient.

Edinburgh (two days)—Royal Infirmary (M. Oliver and colleagues)—Intensive care of the coronary patient, including organization, monitoring and nursing.

The course is open to senior medical practitioners and medically qualified hospital administrators who wish to become further acquainted with recent advances in this field. There are vacancies for 20 members. The fee is approximately $264 which includes the cost of lectures, excursions during the course, hotel accommodation and two meals in London, and full board elsewhere. Applications should be made to The British Council, 80 Elgin Street, Ottawa, Ontario, and must be received in London by July 1, 1971.

when laxatives are unwise
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Surfak is a safe, effective fecal softener which prevents the formation of hard, dry stools thus reducing pain and discomfort, undue straining and irritation. **Surfak** is *not* a laxative . . . it acts solely to permit normal bowel function by preventing the formation of hard, dry stools.
Composition: Each capsule contains 50 mg. or 240 mg. of dioctyl calcium sulfosuccinate. **Indications:** Prevention and treatment of constipation, especially in hemorrhoids, anal fissures, geriatrics, pediatrics, immobilized patients, pregnancy, following anorectal surgery, ulcerative colitis, diverticulitis, and to avert straining after abdominal surgery, in cardiac patients and hypertensive patients. **Contraindications:** None known. **Precautions:** None known. **Adverse effects:** Mild, transitory cramping pains may rarely occur. **Dosage:** Usual adult dose is 240 mg. daily; children and adults with minimal needs, 50 to 150 mg. daily. **Supply:** Red, soft gelatin 240 mg. capsules in bottles of 100; orange, soft gelatin 50 mg. capsules in bottles of 100.

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The rapid bactericidal action attained with Kantrex permits its use in severe infections before culture results are known. Its rapid absorption and diffusion facilitate penetration to infection sites throughout the body for prompt therapeutic response—usually in 24-48 hours—and remission usually within 5-7 days.

Prompt use of Kantrex in *Klebsiella pneumonia* may save a lung or a life. Prompt use in pyelonephritis may reduce renal destruction so often seen in Proteus infections. Prompt use in bacteremia may prevent impending shock and fatality.

New dosage guidelines assure low risk of toxicity. A simple basic dose of 7.5 mg./Kg./I.M. applies to *all* patients on Kantrex therapy. In patients with normal renal function, Kantrex injections are given twice a day; when renal impairment is present, the dose remains the same but the time interval between doses is increased depending upon the serum creatinine concentrations of the patient.

To calculate the time interval between the first and succeeding doses of Kantrex in patients with decreased renal function, simply multiply the mg. of creatinine x 9—e.g. if serum creatinine levels are 2 mg./100 ml., the dosage interval should be 2 x 9 = 18 hours between Kantrex doses.

In anuric adults give 7.5 mg./Kg./I.M. as a single loading dose. In adults on hemodialysis, 7.5 mg./Kg./I.M. every other dialysis.

To avoid ototoxicity, daily Kantrex dosage should not exceed 1.5 Gm. and total therapy should not exceed 15 Gm. or 10 days.

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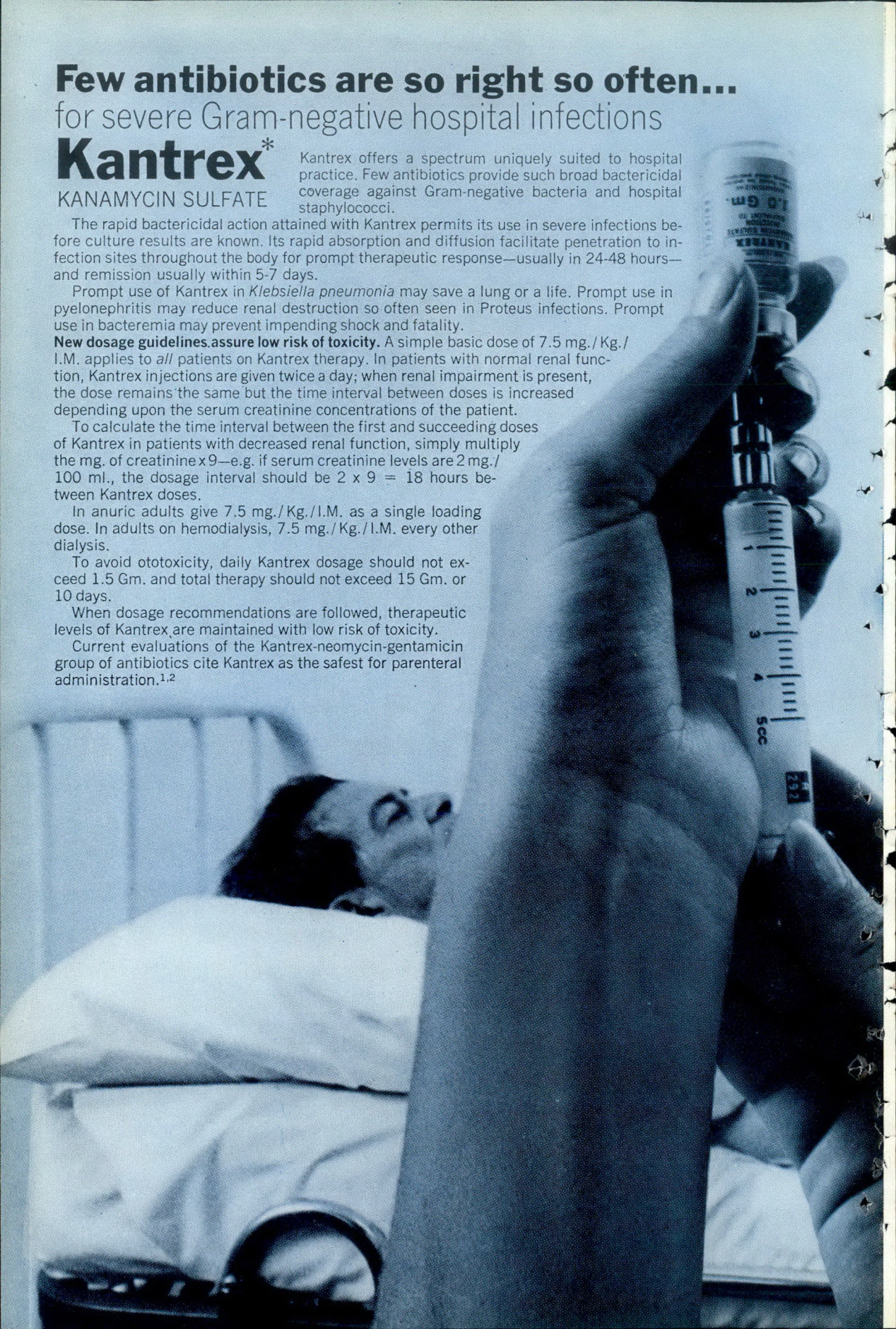
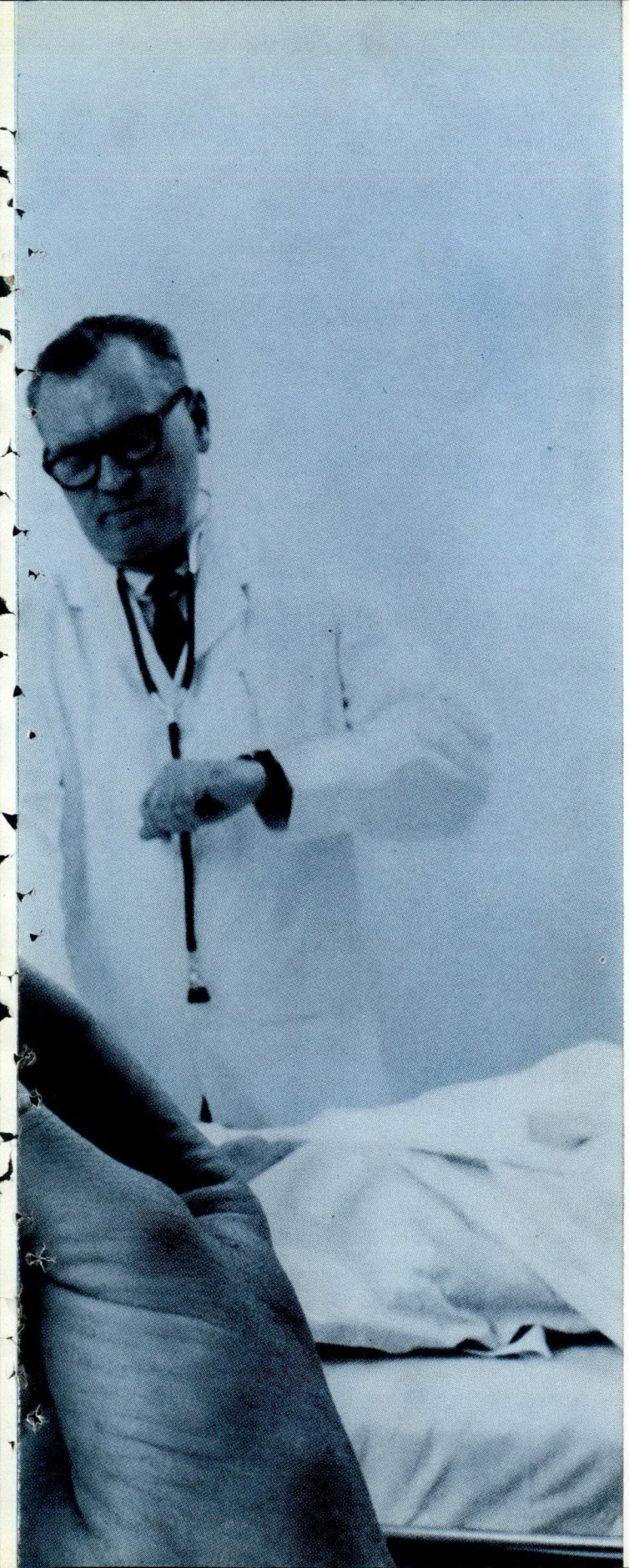
Current evaluations of the Kantrex-neomycin-gentamicin group of antibiotics cite Kantrex as the safest for parenteral administration.[1,2]





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Injection

PRESCRIBING INFORMATION. For complete information, consult Package Circular.

Indications: Infections of the urinary, respiratory and gastrointestinal tracts and of skin, soft tissues, bone periosteum and blood due to sensitive organisms.

Contraindications: A history of hypersensitivity to the drug. Prior auditory damage by kanamycin or other agents may be a contraindication if effective alternative therapy is available.

Warnings: Renal malfunction can cause abnormally high serum levels of kanamycin—assess renal function periodically both before and during therapy. If renal insufficiency exists, decrease the size and frequency of dosages. Discontinue kanamycin and check hearing if azotemia increases. In older patients and patients receiving a total dose in excess of 15 Grams, watch carefully for signs of ototoxicity.

Precautions: If mycotic or bacterial superinfection occurs, discontinue kanamycin and initiate appropriate therapy. Cumulative ototoxic effects may be produced by concurrent or consecutive use of other ototoxic drugs. High doses may cause irritation at infection sites. The drug *should not* be physically mixed with other antimicrobials.

Adverse Reactions: Severe, irreversible hearing loss can occur. Stop therapy if tinnitus or hearing loss occur. Signs of renal irritation may occur (casts, cells, proteinuria). If renal function is normal such irritation is reversible and is not necessarily an indication for stopping therapy. Skin eruptions have been noted rarely. To avoid respiratory depression, postpone intraperitoneal instillation in postoperative patients until recovery from anesthesia and muscle relaxants is complete.

Usual Dosage: 15 mg./Kg./day I.M. in divided doses preferably at 12-hour intervals. Average adult dose is 1 Gram daily. Do not exceed 1.5 Gram even in the heaviest patients. Reduce size and frequency of dosages when renal insufficiency is present. Patients should be well hydrated to minimize renal irritation. Inject deeply into the upper wall, outer quadrant of the gluteal muscle.

Supplied: Rubber capped vials as a ready-to-use sterile aqueous solution in two concentrations: 0.5 Gm. in 2 ml. 1.0 Gm. in 3 ml. *Also Available*—Pediatric Injection 75 mg. in 2 ml.

Complete prescribing information available on request.

References: 1. Finegold, S.M., *et al.:* California Med. *111*:362 (Nov.) 1969. 2. Riley, H.D., Jr.: Pediatrics 1970, New York, Medical World News, 1970 pp. 16-18.

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