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James A. Gray.
27th May 1958.

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RES MEDICA

THE JOURNAL OF THE ROYAL MEDICAL SOCIETY

Editor: J. A. GRAY

Editorial Committee: F. COCKBURN, A. W. DELLIPIANI, and C. V. RUCKLEY

The Royal Medical Society To-day

We have often heard that our University, with its paucity of halls of residence and common rooms used for the right purpose, is fast developing the atmosphere of a huge and impersonal technical college. The undergraduate, his brain dulled by the heavy aroma of haddock, emerges each morning from his "digs". He returns in the early evening to decipher a sheaf of laboriously scribbled notes that might even be headed by the "good morning, ladies and gentlemen" with which his lecturer aroused him from complete coma into the semi-conscious state in which the rest of his day is spent. He has contributed nothing to, and has gained nothing from his day at the "University."

It is perhaps here that the R.M.S. can play its most important role by helping to fill this yawning gap in our undergraduate days with something intangible, but nonetheless lasting for that. No one would pretend that this Society can cure apathy or provide a panacea for every student's problems. Nor is it intended that this Journal should become a medium of propaganda and advertisement. But when this unique Society is actively supported by only a fraction of the undergraduate population, there is room for self-examination on both sides.

Why does the majority of students not belong to the Society? Surely financial reasons cannot be considered when the present day undergraduate thinks nothing of dissipating in the course of one evening a sum that would entitle him to a year's membership of the Royal Medical Society. Does the student not learn of the Society's existence until other University pursuits have won his heart and he cannot afford the time to serve more than one master? This may well be, for in the natural course of events it is the senior student who runs the Society now that the rigours of the pre-registration year have taken this honour from the newly qualified doctor. In their clinical aura senior students are often out of touch with their junior brethren; besides the tenor of debate in the R.M.S. is less attractive to the pre-clinical student since it is more closely geared to the needs of the senior undergraduate.

Some consider that the Achilles' heel of the R.M.S. is its refusal to move with the times; that pompous formality and etiquette were in keeping with the elegance of eighteenth century Edinburgh but have no place in modern times. Sir Robert Hutchison (then Dr Hutchison) indicated in his famous Inaugural Address of 1912, however, that either the proceedings must degenerate into a rag in the absence of a certain amount of dignity or else, with the inhibitory influence of a senior medical man in the hall, the debate must lose its freshness and spontaneity.

Whilst the privilege of unrestricted undergraduate debate in Private Business is to be cherished, guidance from and contact with teachers and

lecturers is much welcomed at the Public Business meetings of the Society and within the pages of this Journal. Some undergraduates outwith the Society contend, perhaps with a note of jealousy, that it exists solely to promote closer contact of a few privileged Members with the teaching hierarchy. The Society has every intention of doing this, but on a much wider scale which will also allow the more junior Members to benefit from the liaison. In this University where the lecturer's bench is so often an insuperable barrier, any means of furthering student-staff relations is surely assisting a worthwhile cause, particularly at a time when changes in the curriculum and format of teaching are imminent.

Finally, the R.M.S. has been criticised for remaining aloof and as it were upon a pinnacle separated from other undergraduate organisations in the University. Such a situation is regrettable but, as is customary, there are two sides to the question. Firstly, membership is not confined to students nor even to medical men and, secondly, the R.M.S. is not a University Society, although it depends on the Faculty of Medicine for the vast majority of its Members. On the other hand, the Society would be the first to acknowledge the long record of co-operation which has existed between the University and itself; besides it is grateful for the readiness of members of the staff to assist the Society in any way they can. Whilst healthy relations exist between the R.M.S. and the staff, it is then unfortunate that a greater proportion of undergraduates cannot reap the fruits of this union. Closer linkage with the Students' Representative Council and its Medical Faculty Committee is therefore not only desirable but in keeping with the spirit of tradition. Although the Society must always maintain its individual identity together with both financial and legislative independence, it can surely be gracious enough to maintain friendly relations with fellow students and their representatives. Perish the thought that either stands to gain nothing from such a union; both stand to lose much by secession.

So much for the negative pan of the balance. What of the positive? The content of Dr Hutchison's Address of 1912 still applies to-day and much of what he prophesied has come true. The Society's Library has seen great changes during the last few sessions and will, within the forseeable future, be fully catalogued due to the enthusiasm and energy of successive *Librorum Custodes* and the generosity of the Carnegie Trust. The enlargement of the Museum with new specimens, microscopes and slides is due to the kindness of the Professor of Pathology. Besides after the installation of suitable heaters in the reading rooms it is hoped that more Members will be encouraged to use the Society's premises during the week.

Friday evenings in Autumn and Spring, however, remain as always the Society's highlight. Dissertations still provide the student with an opportunity of reversing that "criticism of medical education to-day that it makes the student too receptive and insufficiently productive". The ensuing article on Sir J. Y. Simpson verifies Dr Hutchison's words "how often the child has been the father of the man, and the subject which was first brought forward here has been the foundation of a great life work." The recent and controversial television programmes further exemplify Dr Hutchison's emphasis of the importance of exposition and self-expression often first cultivated through discussions in the Society's Hall. "The doctor is no longer merely a private and confidential adviser, he is becoming a public guide, counsellor and friend as well . . . "

At a time when religions, cultures and individuals are menaced by nuclear weapons and foreign ideologies, living traditions assume an importance never envisaged by their inaugurators. Let us then foster unity and friendship and be worthy heirs of our heritage.

THE CONCEPTUAL BASIS OF MODERN SURGERY

By JOHN BRUCE
C.B.E., T.D., P.R.C.S.Ed., F.A.C.S.(Hons.)
Regius Professor of Clinical Surgery in the University of Edinburgh

The broad pattern of surgical practice as we know it to-day was largely designed in the fifty years that centred on the turn of the century. This was a time of great vigour and high accomplishment, when surgical adventurers the world over were ready to exploit to the full the twin discoveries of anaesthesia and antisepsis. It was the era of the "anatomical" surgeon, and speed and manual dexterity wedded to courage and imagination were the qualities that led to success and fame—and fortune. It is small wonder that some came to believe that with their definition of the possible and impossible the ultimate goal of surgery had been attained.

The truth is otherwise; for though much was achieved, surgery was still largely a craft and much of its practice was empirical and ill-conceived. Nevertheless, the debt of the modern surgeon to his immediate ancestors is a substantial one. The experience and the knowledge that they gathered and disseminated has become for all time an important part of the fabric of surgical practice, though in our pride and our satisfaction in the surgery of to-day we are apt to forget it or ignore it or minimise it.

The surgical endeavours of the early decades of this century were in general mainly concerned with the removal of diseased structures and the correction of simple deformities. But since then, and especially during and since the war, a revolution has occurred in both the concepts and the practical content of surgery. This is the result of the permeation of surgical thought and practice by a scientific and experimental outlook, and in consequence fundamental advances both in the ancillary disciplines and in scientific clinical research have enormously increased the scope and the direction of surgical enterprise.

The surgery of to-day may, for want of a better term, be described as "physiological". Possibly biological is more apt, for biophysics and biochemistry, pathology and bacteriology have each made distinguished and important contributions. It is sometimes claimed, indeed, that the surgeon himself has added least; but this is a charge that is easily rebutted. In the event, and almost without exception, it has been the surgeon who has recognised the potential significance of new discoveries in the collateral sciences, and who has integrated them into current surgical practice. Furthermore the ambition—or the inquisitiveness—of the surgeon has often provided a spur to the research worker in the basic scientific departments.

It is manifestly impossible in short compass to scrutinise the many new facets of present day surgery. In this brief contribution I propose only to glance for a moment, and in a general way, at some of the newer concepts on which it is founded, and that have contributed to the greater safety as well as the increased scope of the modern surgical operation.

The most fundamental of these concepts is that no matter how imperative, no matter how life-saving, every operation is in fact itself a form of injury and as such evokes a characteristic disturbance in the physiological and metabolic equilibrium of the patient. Claude Bernard laid the foundations of this knowledge with his definition of the *milieu intérieur*, but it was the

fertile brain of Leriche that completed the concept of a *maladie post-opératoire*, with its implications that to cure by surgical means we are condemned to inflict a hurt that can be insupportable if the disease itself has already exerted a maximum toll. It is the principal object of our pre-operative management to anticipate it and prepare for it; it is our duty, in the course of operation, to minimise the extent of this inevitable injury; and in the days after operation it is our concern not to embarrass the efforts by which the body seeks to compensate, and to effect its own repair.

Fortunately, the biochemical and endocrine resources of the body are well able to restore metabolic balance unless the disease itself, or some post-operative complication, renders the situation difficult. The dangers as well as the benefits of blood—of water—of salt—of potassium—would each make an admirable topic for surgical homily; and such a therapeutic slogan as "push fluids", a not infrequent catchword of a year or two ago, is dangerous counsel, unless fluids represent the particular need at the particular moment.

The mechanisms by which these post-operative metabolic changes are brought to pass are by no means clear. The evidence suggests that the pathways are endocrine—the posterior pituitary and its antidiuretic hormone in the case of water, the adrenal cortex and its hormones in the case of sodium, potassium and nitrogen. On the other hand the purpose of the metabolic response to surgery is reasonably clear. The alterations in electrolyte and nitrogen metabolism conserve the body fluids and establish the conditions necessary for the formation of the inflammatory exudate, and for the processes of repair. There is no call for therapeutic interference, therefore, unless the "normal" losses of fluid and electrolyte are increased by such abnormal losses as by intestinal suction, or unless for any reason the resumption of a balanced diet is delayed.

After much heart-burning, we have in fact reached a safe and satisfactory working policy. We have relearned that if we do not interfere, the average patient recovers from operation without our assistance, unless the circumstances of his illness or his convalescence are in some way abnormal—as in the case of intestinal fistula, prolonged gastric suction, or the continued discharge from a suppurating lesion.

I suspect that some of our "problem cases" have been and are of our own making; and it is common experience that a satisfactory technical operation is not often followed by serious difficulty. For my own part, I subscribe whole-heartedly to Maddock's dictum—"that with the best of experimental evidence at hand to-day, the immediate post-operative period calls for only moderate amounts of fluid, and no electrolytes unless abnormal extrarenal losses are occurring."

Apart from these inescapable metabolic disturbances the most evident of the other effects of surgery is to cause the loss of a variable quantity of blood; and blood loss—excessive, or, in the previously anaemic, even within the usual limits—is fundamentally the cause of surgical shock. It would be idle to pretend that we know all there is to know about shock, or that it has been abolished from the surgical scene; but our concepts of its effective management are gradually being clarified. Obviously it is desirable to correct anaemia and blood deficit before operation, when they are detected; but in some circumstances the volume of circulating blood may be seriously reduced without appreciable change in the results of our standard blood examination. This is especially so in the elderly, and in those with malignant disease, especially of the alimentary tract. It has been shown that in them—and they form an increasing number of our surgical patients—that blood counts, haemoglobin estimations, and haematocrit readings do

not always accurately reflect the *mass* of blood in the circulation, which can only be determined by measurement of the total blood volume.

Until recently, estimation of blood volume was by tedious and unreliable dye methods; but the use of isotopes such as I^{131} tagged to the serum albumen or of chromium-labelled red cells has made its assessment simple and reasonably quick. Using these techniques it is obvious how often in the past our pre-operative preparation has been inadequate in respect of blood restoration. Clinical instinct has suggested this, for surgeons of experience have often paused by a bedside, convinced that a patient was in need of blood, only to be confronted with laboratory evidence apparently to the contrary.

The amount of blood spilt during operation is largely a matter of operative technique. Dissection in correct anatomical planes, control of the main arterial supply at an early stage of extensive procedures—of the internal iliacs in abdomino-perineal resections, for example—and patient, gentle and unhurried haemostasis, will reduce blood loss to an inevitable minimum, and operative shock to consequent insignificance.

It should be simple to calculate and to replace the blood lost during operations; and yet our estimates are almost always too low. In the course of an uncomplicated gastrectomy, the average loss is something of the nature of half a litre per hour, and the circulatory volume is further depleted by sweating and by insensible excretion. Deficits of this order are easily and rapidly compensated for without assistance; greater losses in more extensive procedures demand energetic replacement, not later, but at the time of operation. If this is not done the body does its best to compensate by constriction of the peripheral vessels—a dangerous remedy, since the consequent ischaemia and hypoxia, if protracted, may cause permanent damage to the brain or the viscera, particularly in the elderly. There is some evidence that the ischaemic liver releases a vaso-depressor substance, which causes widespread vascular paralysis and irreversible shock; but even if the immediate shock appears to be relieved by later transfusion, death may take place within a few days from suppression of renal or hepatic function.

Naturally the difficulty of estimating blood loss is greatest after injury. Experience in the Korean War confirmed the impression of World War II that enormous quantities of blood were necessary after severe trauma—much more than appeared necessary by former standards. Under-assessment, in fact, is almost invariable; the corollary is important, namely that lack of response to apparently adequate quantities of blood should usually be the signal for even more energetic transfusion.

The limited "life" of stored blood, the difficulty of its transport over long distances and the realisation that the amounts needed to restore a "depleted" peripheral circulation can be considerable have together stimulated a search for substitutes and alternatives. The development of methods of separating and drying the plasma of effete stored blood seemed to provide the ideal "plasma expander". Unfortunately, the high incidence of serum-transmitted diseases such as infective hepatitis in those transfused both by wet plasma and rehydrated dried plasma caused its use to be abandoned, and provoked a successful search for artificial plasma substitutes, such as Dextran. But the recent demonstration that even virus-infected plasma can be rendered safe by exposure to room temperature at intervals appears to make its use justifiable again.

Developments in the art and practice of anaesthesia have greatly assisted the modern surgeon in his efforts to stabilise the physiological status of the patient undergoing operation. Relaxants have made deep anaesthesia un-

necessary and allowed the use of anaesthetic agents which are much less toxic, less productive of shock and less attended by post-operative crises.

In the prevention of shock the anaesthetist of to-day can contribute enormously towards the diminution of blood loss by inducing a state of deliberate hypotension during the operation. This he can accomplish in one of several ways—by hypotensive drugs, by high spinal anaesthesia that blockades the vasoconstrictor government of the peripheral vessels or by arteriotomy and the actual withdrawal of blood.

My own experience has been mainly with the second of these methods. High spinal anaesthesia results in a state of generalised vascular dilatation; the peripheral resistance is accordingly eliminated, and a fall in blood pressure results. By suitable postural adjustments—so that the operative field is at its highest level—the tissues can be rendered virtually bloodless, and surgical dissection is made easier as well as safer.

Enlightened management of the metabolic sequelae of operation, the advances in the techniques of anaesthesia, our ability, for most practical purposes, to control shock, and the elimination, for the most part, of the hazards of infection by chemotherapy and antibiotics have made possible surgical intervention in diseases formerly beyond the surgical horizon; and the opportunities have expanded for increasingly extensive surgery in malignant disease—of the pancreas, the pelvic organs, the lung, the stomach and the liver. Once on the frontier of surgical endeavour these mighty enterprises have become almost commonplace.

The importance of adequate nourishment in furthering healing and promoting recovery has long been appreciated, and yet the nutritional care of the surgical patient has become the subject of serious study, only in recent years; and this despite the fact that in most diseases, the protein reserves of the body are more often and more seriously depleted than water and salts. The effects of protein deficiency are diverse, and threaten the success of operation at many points—a predisposition to shock, an increased vulnerability of intestinal and external suture lines, and a tendency to the development of wound sepsis. It is not always possible to restore the undernourished victim of malignant disease to positive nitrogen balance, or to compensate for the phase of nitrogen catabolism after operation. But much can be, and is being accomplished in the management of the seriously burned, the gravely injured, and those suffering from such wasting diseases as ulcerative colitis, in all of which there is a continuing long-term drain on the body stores of nitrogen, potassium and fat.

In burns, a regimen of supplementary feeding by mouth or tube with specially prepared diets, reinforced by fat emulsions, has been used by my Edinburgh colleagues, Anne Sutherland and A. B. Wallace. They have shown that if this programme is started as soon as the initial period of fluid replacement is completed, it is possible to have such patients at or above their normal weight on discharge; and during their time in hospital, their general condition is excellent, grafts "take" better, epithelialisation of raw surfaces is more rapid, and the need for blood transfusion is reduced.

Burns best typify the metabolic problems of severe injury; in ulcerative colitis the surgeon encounters an essentially similar problem as a sequel to disease. Formerly the emaciated, querulous and dispirited patient was ill-equipped even for operation in stages, and the mortality from surgery was forbidding. To-day the situation is quite changed, and largely because we have come to conceive the problem as one almost entirely of restoring electrolyte balance, and satisfactory nutritional status.

Thus, measurement of the volume of the stool, a useful and neglected examination, may reveal a fluid loss of more than 2 litres a day, with

corresponding deficits in electrolytes, and especially potassium. But the extent of the protein loss is even more important. This loss is two-fold. As in any febrile disease, there is the usual loss of nitrogen from protein breakdown, except that in ulcerative colitis the fever may be protracted. Coupled with diminished intake of protein, this means a negative nitrogen balance and an inevitable fall in weight. But there is a second loss whose extent has been overlooked in the past, and that is the protein exudate from the inflamed bowel itself. The amount of this may be very great, and goes far to explain the rapid deterioration that accompanies the florid stages of the disease. Measurement of the stool protein as an index of this loss has been little used, but in our hands it has become an indispensable investigation. We have recorded losses in the stool of well over 50 g. of protein in 24 hours; and the nutritional problem therefore is almost identical to that of the severe burn. Remission is impossible, and the ulcerated bowel cannot even begin to heal, until the negative nitrogen balance is corrected; and resort to operation in such circumstances is foredoomed to failure. There is no doubt that cortisone therapy often imitates the process of remission; but part at least of its good effect is to induce an euphoric state in which the conduct of an energetic campaign of protein feeding is simplified.

So far, my report is of a steady advance in the direction of increased safety in the technical exercises of surgery. But surgical progress has not been confined to this; there have been notable developments in relation to the cause and management of certain of the diseases that seemed to offer an almost insoluble challenge.

Of particular interest are the newer concepts of cancer. In the last few years it has become abundantly clear that the growth of some cancers of the breast and of the prostate can be influenced by the administration of naturally-occurring hormones, or by altering the hormonal status of the individual by the removal of certain endocrine glands. In other words, a disease for long regarded by the pathologists as the autonomous, unfettered and uncontrolled proliferation of cells that had become "lunatic" is now discovered to be subject at times to mechanisms or influences that arise naturally within the body. It is certain that as knowledge advances such crude attempts to adjust the endocrine status as adrenalectomy and removal of the hypophysis will pass into limbo. But what an exciting avenue of research these tentative efforts have opened! Will it ultimately transpire that other tumours are dependent on other body secretions, or other hormones? Will the property of malignancy in cells ultimately prove to be only a small qualitative difference—chemical or enzymatic—from the normal? Is this a gleam on a horizon for long obscured in gloom? If so, we must

> "Adventure on, for from the littlest clue
> Has come whatever worth man ever knew."

The perimeters of surgery are in fact steadily widening; but in addition there are exciting salients in advance of the expanding front. These have as their objective not the removal of more and more diseased tissues—the surgery of ablation—but their repair, or their substitution when past salvage.

The replacement of damaged or lost or destroyed tissues by counterparts from another individual or by artificial substitutes is hardly new. Blood transfusion and bone-grafting are well-established methods of tissue-replacement. So too is skin-grafting. But skin-grafting has unleashed a host of problems of fundamental biological importance. Skin transplanted from one individual to another survives for a short period and then dies, unless the transplant is from one identical twin to another. The mechanisms responsible are obviously immunological, for a second transplant from the

same donor to the same recipient is even more quickly destroyed. That the rejection of such homografts is a matter of genetic architecture is evidenced by the survival of grafts between individuals of the same genetic constitution (identical twins); and a difficult though hopeful field of research has been opened up in an attempt to determine the mechanisms involved and the means by which they may be circumvented. This is obviously a matter of great practical importance. Skin can now be stored in banks as readily as bone and blood, but its usefulness is limited to providing a very temporary epithelial cover in severe skin loss, or in burns. Its permanent survival would greatly extend its range of usefulness. There is at least an indication that we are coming to grips with the problem. My colleague Professor Woodruff has shown that in rats tolerance to homografts can be induced by injecting the newborn with cells from the future donor, and this work has been confirmed by others. Indeed, it seems that tolerance to heterografts can also be increased by this technique; and although at the moment these studies have no immediate practical application, they indicate that the difficulties of homografting are within reasonable sight of resolution.

Organ transplants behave in a similar fashion to skin. But if they can be given a blood supply, they may function for a time (or indefinitely in the case of identical twins), and there are now several cases on record in which a kidney has been donated from one twin to another. The place of such heroic measures in surgery is probably very limited; but one form of homograft appears destined to have a permanent place in our repertoire. Excision of segments of diseased or damaged blood-vessels has now an established place in the management of peripheral vascular disease and injury. Cadaver vessel grafts (and even artificial prostheses) are for a time, at least, both effective substitutes for the resected segment, though their ultimate place in surgical therapy has still to be determined.

The most fascinating of the growing edges of surgery is that of the operative treatment of disease of the heart and the great vessels. This has already made rapid strides; for though it is more than 30 years ago since Henry Souttar of the London Hospital first relieved a mitral stenosis by digital dilatation, and though Beck and O'Shaughnessy in the 1930's had striven to relieve the ischaemic heart by establishing a new blood supply, the foundations of the modern surgery of the heart were laid by Alfred Blalock and Helen Taussig only a decade ago. Blalock's operation for the blue babies of Fallot's tetralogy was catalytic; in its train has followed the surgery of the mitral valve, the aortic valve, and to crown all the surgery of the congenital intra-cardiac deformities.

The manner in which this last advance has been achieved is proof of the virility of modern surgery. The manipulations demanded for the correction of most intra-cardiac lesions require arrest of the heart and of the circulation through it for too long a period to be compatible with the survival of the brain, and the avoidance of hurt in other vital organs. The solution of this difficult problem has followed two main lines—refrigeration, and the development of an extra-corporeal circulation.

The practice of refrigeration depends on the fact that the lower the temperature to which they are exposed the smaller the amount of oxygen required for survival by living tissues. The organs most vulnerable to hypoxia are the brain and the heart itself; but when exposed to a temperature of 26° C, their circulation can be arrested for up to 20 minutes which is long enough for most corrective procedures within the heart cavity.

Unfortunately hypothermia has the serious drawback of tending to retard or prevent the recovery from ventricular fibrillation, which is one of the

most serious of the hazards of cardiac surgery. And so it will probably prove inferior to methods of bypassing the heart by means of "heart-lung" machines. But for operations on the great vessels, when it may be necessary (in the excision of an abdominal aneurysm, for example) to arrest for a time the blood supply to the kidney, the liver, or the spinal cord, refrigeration is ideal, since these procedures do not carry the same risk of fibrillation.

The "heart-lung" apparatus represents a triumph of co-operation between the clinician, the physiologist and the engineer. The principle behind the several bypass machines is to withdraw the venous blood from the great veins near the heart, pass it through an artificial oxygenator that replaces the function of the lungs, and then pump it back into the aorta, thus making it possible to exclude the heart during the time required for intra-cardiac manipulations. Not all the problems posed by these complicated techniques have been resolved, but already the scope of cardiac surgery has been notably extended, and it is only a matter of time before the present difficulties are overcome.

There is much else one could say about contemporary surgery but limitations of space allow only a final reflection. It is this: that though there are many dark places to be illumined and much still to be accomplished the physiological approach to surgical problems has already inspired concepts and principles that are fundamental, and accurate, and destined to find a permanent place in surgical thought and practice.

SOME PATHOLOGICAL ASPECTS OF DISSECTING ANEURYSM

Based upon a Dissertation on "Dissecting Aneurysm" given before the Society on Friday, 17th January 1958.

By M. J. MACLEAN

The term dissecting aneurysm implies the development of a circulatory pathway between the layers of the vessel wall. It can occur at all ages and in both sexes, being most frequent in men, in the fourth, fifth, and sixth decades, and in women in the eighth and ninth decades. It does not occur in normal arteries.

Aetiology

The aetiological factors are variable and largely hypothetical but the following theories appear to have substantiating evidence of their authenticity:

(1) **The mechanical theory.** Physical and mental strain causing a sudden increase in blood pressure is sufficient to produce the medial rupture leading to dissecting aneurysm only when the vessel wall is diseased. About 40 per cent. occur after mild exertion, although this as an aetiological factor is disputed by others. Hypertension which may be of the essential variety but is usually of renal origin is present in over half the cases. Mechanical injuries such as violence and traumatic accidents probably do not produce dissection.

(2) **Congenital deformities,** including coarctation, bicuspid aortic valves, and hypoplasia. 16 per cent. of cases of coarctation of the aorta develop dissecting aneurysm.

(3) **Pregnancy.** In 83 per cent. of one series of investigations, dissection occurred antepartum and thus cannot be attributed to the strains and blood pressure changes occurring during labour.

(4) **Diseased aortic wall.** Disease of the intima rarely causes dissecting aneurysm and those beginning at atheromatous plaques or ulcers are usually restricted in extent. An abnormal tunica media may arise through disease of the vasa vasorum or be essential in character. The degeneration, which may be local or diffuse, is a chromatotrophic or mucinous process probably involutional or senescent in nature and it may progress to cyst formation. There is no connection between syphilitic mesaortitis and dissecting aneurysm and the joint occurrence of the two conditions is merely coincidental. Since the reaction of human tissue to the *Treponema pallidum* is mainly one of fibrosis, the lesion in the aortic wall is localised rather than generalised.

Pathology

The primary rent in the aneurysm, usually a few centimetres in length, occurs in the aortic intima which is usually normal at the site of the tear. This would suggest that the tear is an effect rather than a cause of dissection. The most frequent sites of the tear are, firstly, the ascending aorta, accounting for 50 per cent.. of cases of dissection, secondly, the junction of ascending and transverse portions for 20 per cent., and thirdly, the junction of transverse and descending portions for 10 per cent., the dissection being in the descending thoracic or abdominal aorta. The length of the dissection

varies from a few centimetres to the entire length of the aorta, occasionally extending down as far as the popliteal arteries.

After the tear blood penetrates radially to a point between the outer and middle thirds of the aortic wall and a cleavage plane is created between the elastic laminae. Dissection usually continues in the direction of intraluminal flow but may be directed towards the heart, particularly in the first two groups, for 10 per cent. of the ruptures in those situations do so. Secondary rupture may occur along the aortic wall either back into the lumen or more frequently outwards, with fatal results.

The pathological lesion may be of several distinct types. Common to the great majority of instances is a process which is independent of the changes in the vasa vasorum or the intimal coat of the aorta and which is unaccompanied by cellular inflammatory changes. When reacting cells are present they are usually few and appear to be secondary to the degenerative process. This degeneration is much more marked than is the normal loss of smooth muscle with age. The outer third of the media contains the largest number of smooth muscle cells, which is worthy of note for it is in this outer third of the media that cystic areas, in which all the elements are degenerated, are so often found.

The various types of medial lesions that have been observed in this process, referred to as medionecrosis, are as follows:

(1) Primary degeneration of the elastic lamellae may occur in the form of a fatty metamorphosis, fragmentation, or necrosis, with some damage to the supporting collagen or muscle fibres, with or without mucoid accumulation, or

(2) Sometimes hyaline degeneration of the interlamellar connective tissue takes place, or

(3) Non-exudative necrosis of muscle cells proceeding from simple nuclear loss to extensive structureless homogenisation of the muscle cells and the adjacent collagen and elastic fibres, with or without mucoid accumulation, and

(4) Primary over-production of mucoid substance in the interlamellar ground substance with encroachment over the muscle, elastic and collagen fibres, with the ultimate development of cysts.

An actual quantitative reduction of the medial tissue elements linked with marked thinning of the vessel wall, may be associated with any of the preceding degenerative lesions, a process often found in Marfan's syndrome and thought to be an inherited mesodermal defect. In cases in which pronounced mucoid accumulation with cyst formation is observed these appear most often to involve the thoracic aorta, particularly the ascending portion of the arch.

Areas of destruction of medial tissue may be replaced by poorly vascularised fibrous scars or by regenerated muscle or elastic tissue. The removal of necrotic tissue is effected through a humoral route and some acellular zones of necrosis show no tendency at all towards replacement by a substitute tissue.

Pathogenesis

The mode of production or development of the disease can be found in the answers to three questions:

(1) What factors determine the rupture and the site of rupture of the tunica intima?

(2) What factors lead to the degeneration of the media?

(3) What factors determine the final course of the dissecting process, either out through the tunica adventitia or back through the tunica intima?

Dealing firstly with the mechanics of the initial intimal tear, the influence of an actively contracting hypertrophied left ventricle in producing a high systolic blood pressure is evident, and has to be accepted as an important factor in elongating and distending the aorta, especially in its ascending part. Moreover the direction of the blood stream is altered quite suddenly as it passes from ascending to transverse part, and again from transverse to descending portion, so that the wall of the vessel has to withstand a greater strain than elsewhere. This should be more marked on the greater curvature of the aorta than on its lesser curvature. The systolic propulsive force which is exerted chiefly longitudinally, parallel to the axis of the lumen, will have greater effect in elongating the vessel if any irregularities are present like atheromatous plaques on the inner surface which will increase frictional resistance.

Such irregularities are not as common in the ascending aorta as in the transverse and descending portions; but on the other hand primary rupture occurs much more commonly in the ascending aorta than at the junction with the transverse part or in any part of the extrapericardial aorta. This can be attributed to two reasons. Firstly, the longitudinal force is greatest in the ascending portion, as is borne out by the frequency of circumferential tears in this region, for the direction of the linear tear will be perpendicular to the direction of the preponderant stretch. Secondly, the abrupt diastolic recoil meeting the resistance of the closed aortic valves is of even greater importance as a factor in producing the primary tear. In diastole on closure of the valve, the longitudinal force is largely converted into a transverse one with consequent lateral stretching of the intrapericardial aorta. Additional factors are the resistance offered by the distended pulmonary artery and by the rigid attachment of the pericardium at its reflection, both of these tending to increase the strain which has to be borne by the intrapericardial aorta.

In consideration of the second question, the factors producing the degeneration of the media, we find that the cause of cystic medionecrosis is still unknown. Medionecrosis of the aorta has been produced experimentally in rabbits using the intravenous injection of diphtheria toxin. Intravenous tyramine injections also produced medial necrosis in some of the animals. Similarly necrosis has been produced in rats by feeding the sweet pea, the toxic component of which is Beta-amino proprionitrile. A medial degeneration has also been produced in guinea pigs and rabbits by deprivation of Vitamin E. Cystic medionecrosis may be found in patients dying from various causes and there is some association with age but none with sex or hypertension. Cystic necrosis may occur without dissection, but appears to be necessary for its development. It may result from exhaustion of the muscle in its efforts to prevent overdistension of the aorta, or an excess of adrenaline might cause spasm of the vasa vasorum, focal ischaemia and necrosis. Whatever the cause the media generally gives way before the intima.

The factors determining the final course of the dissecting process or secondary rupture are (1) weakness of the outer wall, (2) atheromatous plaques weakening the inner wall, and (3) the presence of normal anatomical structures such as aortic branches which tend to hinder continued dissection. Secondary rupture outwards may occur at any point along the aortic wall, but most frequently into the mediastinum. This occurs in 85 per cent. of cases, the other 15 per cent. dissecting back into the lumen.

The pathogenesis in subjects under the age of forty can generally be attributed to one of the congenital lesions already described. In 50 per cent. of these there is also an abnormality in the connective tissue, but it is unlikely that medionecrosis develops long before dissection occurs.

It is not known whether a true cause and effect relationship exists between pregnancy and dissecting aneurysm but, if it does, it may be due to the hormonal changes which may weaken the aortic wall, rendering it more susceptible to dissection.

Hypertension is usually present in those over forty suffering from dissecting aneurysm. Dissection is, however, rare in cases of malignant hypertension, its incidence being 0·2 per cent. (Beaven and Murphy, 1956). These authors report dissection in nine hypertensive patients being treated with methonium drugs, six of whom were in the malignant phase. Since the incidence is greater than would be expected by chance, some workers have suggested that the methonium compounds might play a role in the aetiology of dissecting aneurysm via the wide fluctuations in blood pressure which occur in therapy, these producing additional stress on the aortic wall. This observation is of value since physicians may mistake this complication for a myocardial infarction, withhold hypotensive therapy which may be of some value, and administer anticoagulants which further reduce the remote chance of survival.

Conclusion

In conclusion, the types of patients liable to develop dissecting aneurysm are:

1. Those with coarctation or extreme hypoplasia of the aorta.
2. A few patients with atherosclerosis of the aorta with ulceration of the intima which permits dissection to begin at this point.
3. Others who develop it through disease of the vasa vasorum of unknown aetiology with weakening of the media.
4. In the majority of cases no aetiological factor is found. They present no specific disease of the aorta, *in the absence of microstudies.*

In brief then, no single causative agent or morbid process can be demonstrated as consistently producing the vascular changes leading to dissection. Death in 70 per cent. of cases occurs from rupture externally, and there is little relation between the site of tear, the length of the dissection, and the time of survival.

CHANGING FASHIONS IN DIABETES

By D. M. DUNLOP
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The increasing tempo of change in outlook and way of life is a characteristic of our modern age, and our changing attitudes in medicine keep pace with the rapid metamorphosis of the intellectual and material world around us. When I was asked to write an article for *Res Medica* on diabetes I thought, therefore, that it might be amusing and instructive to contrast my attitude to the disorder twenty-five years ago when I was a young physician with what it is now when I am a middle-aged or elderly one, for in almost every respect the change has been revolutionary.

Twenty-five years ago we regarded the pathogenesis of diabetes as being very simple, however complicated it might be to treat. We knew that the pancreatectomised animal or the animal poisoned with alloxan became diabetic and died but that it could be kept alive by the appropriate administration of insulin. Diabetes was therefore regarded as being due to a simple deficiency of the internal secretion of the pancreatic islet tissue just as primary myxoedema was due to a simple failure of the thyroid to secrete the thyroid hormone.

We now no longer regard diabetes as being due to the simple failure of this secretory capacity of the beta cells of the islets of Langerhans. Though this may account for some cases it cannot account for all as is shown by the fact that total pancreatectomy in non-diabetics results in a relatively mild diabetes which can be controlled by not more than 40 units of insulin a day, and we know that many diabetics regularly require far larger doses than this. Further, diabetes can be induced by the injection of crude emulsions of the pituitary gland and can be improved by hypophysectomy, and these experimental observations have their clinical analogues in the diabetes of acromegaly and the increased sensitivity to insulin of patients suffering from hypopituitarism. The pituitary growth hormone has been shown to have diabetogenic effects, but the hypophysis also exerts its diabetogenic influence through the stimulant effect of corticotrophin on the adrenal cortical hormones. Thus cortisone given to the hypophysectomised animal or to a patient with hypopituitarism corrects most of the hypoglycaemic effects produced by loss of the pituitary. Further, adrenalectomy or Addison's disease cause a marked tendency to hypoglycaemia and may alleviate a pre-existing diabetes, while adrenal cortical hyperfunction, as seen in Cushing's syndrome, may result in hyperglycaemia. Thus, though the mechanisms responsible for the production and continuance of diabetes remain obscure, there seems little doubt that in many cases lack of insulin is relative rather than absolute. It is probable, therefore, that the term "diabetes mellitus" is a comprehensive one which includes a number of diseases with the common characteristics of hyperglycaemia and glycosuria, just as "anaemia" is a comprehensive term which includes a large variety of disorders characterised by clinical features which are the direct consequence of the diminished oxygen-carrying power of the blood. Indeed,

apart from her mild hyperglycaemia and glycosuria, the obese middle-aged diabetic woman presents few clinical features in common with the young diabetic male: the one suffers from obesity and possibly from pruritus and neuritis, the other from polyuria, thirst, emaciation, weakness, and ketosis.

Though the mechanisms responsible for the failure of the pancreatic internal secetion were obscure we had little doubt, twenty-five years ago, that the failure occurred coincidently with the onset of the symptoms of the disease. We are now more apt to look upon diabetes as a late clinical manifestation of a metabolic abnormality which may in some cases have been operative for many years prior to the onset of the hyperglycaemia and glycosuria with their accompanying symptoms, just as adult tuberculous manifestations may in some cases be the last verse of a song sung to the infant in its cradle. The probability of a preclinical diabetic state is perhaps best exemplified by the obstetrical history of the diabetic woman. As is well known, such women tend to give birth to large babies and there is a high foetal loss rate in diabetic pregnancies, but it is less well appreciated that these same tendencies can be traced in the obstetrical histories of such women for many years before they become clinically diabetic. Thus the foetal loss rate for pre-diabetic periods of twenty years is in excess of the non-diabetic control rate and steadily increases till it reaches a maximum in the five-year period prior to the onset of clinical diabetes. The high incidence of large babies in this pre-diabetic period is also noteworthy. Some 60 per cent. of mothers who eventually become diabetic give birth to babies of 10 lb. or more at some time prior to the onset of their clinical diabetes. Indeed it seems that the heavier the baby the more likely is the mother to develop diabetes, and if she gives birth to an enormous one of 13 lb. the prospects of her developing diabetes are very great.

Thus, it seems that there is a factor conducive to large babies and to foetal and neo-natal mortality which may be active for as long as twenty years prior to the development of clinical diabetes and very active for the five years immediately preceding it. It seems probable that the factor responsible for the high foetal loss rate and the ensuing maternal diabetes has a common basis in some general metabolic disturbance in the mother, and that the development of clinical diabetes is a late manifestation of this disturbance.

Another example of the pre-clinical diabetic state is to be found in the transient diabetes not uncommonly induced in seemingly healthy persons by the development of a severe staphylococcal boil or carbuncle; yet in many such patients their glucose tolerance may apparently return to normal with the subsidence of the infection. The majority, however, develop permanent diabetes in a shorter or longer time.

If we are ever to be able to prevent the onset of clinical diabetes we must be in a position to recognise those who are destined to develop it. The conventional oral glucose tolerance is a rough test which does not give a precise evaluation of glucose tolerance as absorption from the intestine is not completed for a variable time. Thus the rise and fall of the curve do not reflect the true rates of either absorption or disposal as the two processes progress simultaneously. In contrast, following the intravenous administration of glucose, the maximal hyperglycaemia is immediate and the subsequent fall in the blood glucose level is uninfluenced by simultaneous absorption. Analysis of the observed fall in blood glucose by appropriate mathematical methods eliminates a major inaccuracy in the measurement of glucose tolerance and permits it to be expressed in numerical terms. The test can be made even more sensitive by taking advantage of the diabetogenic activity of a single dose of 200 mg. of cortisone administered orally

two hours prior to the injection of glucose. It may be that by the employment of the cortisone loaded intravenous tolerance test the diagnosis of pre-clinical diabetes will be made possible, but it will take years before such expectations can be fully confirmed.

Twenty-five years ago we were entirely occupied, so far as diabetes was concerned, with endeavouring to keep the patient alive for a while and, apart from gangrene, we knew little of its ultimate complications for few patients had lived long enough to develop them. To-day the problem is not so much that of the acute disease as exemplified by diabetic coma, for we know, or ought to know, how to avoid that disaster, as it is of a chronic disorder with a considerable expectation of life which involves a prolonged effort to avoid the chronic degenerative complications which so commonly ensue—retinopathy, nephropathy, neuropathy, and the premature occurrence of cerebral and coronary atherosclerosis.

Thus the common cause of death among young diabetics in most communities which are well organised from a medical point of view is no longer diabetic coma, as it used to be, but uraemia—the result of diabetic nephropathy (the Kimmelstiel-Wilson syndrome). Is the occurrence of these complications to be regarded fatalistically as being due to something inherent in the diabetic process like the large babies of diabetic and pre-diabetic mothers—the inevitable sequel in a shorter or longer time of the diabetic state? Or can they be prevented by care and trouble directed to the control of the metabolic disturbance?

There are many who believe that there is no apparent relationship between the severity of diabetes, the control of the condition by treatment and the presence or absence of complications—that it makes little difference how a diabetic is treated, if he lives long enough he will inevitably develop one or other of them. The protagonists of this view are naturally of the opinion that hyperglycaemia itself does no harm, provided it is not sufficiently gross to cause pruritus or severe polyuria and thirst, and that, provided there is a proper utilisation of carbohydrate, moderate hyperglycaemia and glycosuria do not matter. This led to a revulsion from the extremely meticulous dietetic control of twenty-five years ago to the use of "free diets" in treatment. Patients were allowed to eat what they liked and enough insulin was administered to ensure ample carbohydrate utilisation from the abundant intake. Hyperglycaemia and glycosuria were largely disregarded and the criteria adopted to govern insulin dosage were freedom from hunger, thirst, nocturia, and ketosis, and the maintenance of weight and energy on the one hand and the avoidance of hypoglycaemic reactions on the other. The advocates of this system claim that patients benefit psychologically from this form of treatment through freedom from irksome restrictions imposed upon their daily life; that "each meal which should be an elegant satisfaction of appetite is not turned into a problem in arithmetic and a trial in self-abnegation"; that if complications are inevitable anyway let the patient eat, drink and be merry and control his diabetic symptoms by appropriate amounts of insulin.

The majority of workers, including myself, are now, however, opposed to this point of view. Our experience with "free diets" has been disastrous and we believe that there is a definite correlation between diabetic "control" and the incidence of complications. We believe, therefore, that whatever specific aetiological factors may be causing diabetic complications, the careful control and aggressive treatment of the disorder over the years is an important factor in the prevention or postponement of these complications, and that every effort should be made to restore physiological conditions,

including freedom from glycosuria and a normal blood-glucose concentration as far as this is possible.

Thus the pendulum of medical fashion has tended to swing back again in favour of the careful dietetic control which was in vogue twenty-five years ago, but there are considerable differences in our methods of control. Twenty-five years ago diabetic diets were very low in carbohydrate—seldom containing much more than 100 g. a day—and very high in fat; they were in consequence expensive, highly abnormal, and distasteful to many patients. Nowadays our aim is to give a diet suitable for the particular patient which does not vary much from day to day in its calorie and carbohydrate content so as to match the daily dose of insulin, but in which the carbohydrate is only moderately reduced and the fat only moderately increased. Further, we have come to realise that good control cannot be achieved by urine testing alone but demands frequent estimations of the blood glucose content as well.

A glucose free urine does not necessarily imply a normal blood glucose concentration which we used to think was the case. We then believed that an individual was born with a certain renal threshold for glucose, just as he was born with a certain shape of nose, and that this did not alter throughout life; the great majority of renal thresholds for glucose lay between 160 and 180 mg. of blood glucose per 100 ml.; it was recognised that occasionally a person had a low threshold. We now realise that a diabetic's renal threshold is not fixed for life but may vary greatly from time to time. Thus, in cases of long duration—especially if the patients are atherosclerotic and have been poorly controlled—the renal threshold for glucose frequently rises to considerable heights (300 mg. per 100 ml. or even more in exceptional cases) so that the urine may contain little or no glucose in spite of very significant degrees of hyperglycaemia. On the other hand, some diabetics —particularly pregnant diabetics—develop low renal thresholds for glucose and in them glycosuria may occur in spite of normal blood glucose levels; in such patients any attempt to keep their urine free from glucose is usually followed by hypoglycaemic reactions. Thus, unless the patient's renal threshold for glucose has been ascertained to be approximately normal, efficient treatment cannot be controlled by urine analysis alone, but demands frequent blood glucose estimations as well. The efficient management of the surgical diabetic, the diabetic woman in labour and the patient suffering from diabetic coma also demands facilities for rapid and frequent blood glucose estimations.

Lastly, the treatment of diabetic coma has changed considerably in the last twenty-five years. We realised then as we do now that such patients were profoundly dehydrated and required fluid, but the fluid we gave was glucose-saline; we realised that he required insulin, but the doses we gave tended to be unduly exiguous; and we didn't realise at all that in the recovery phase the patients developed hypokalaemia and were often in desperate need of potassium. Now, we give saline intravenously, at least in the initial stages of treatment instead of glucose-saline; we usually give from 175 to 300 units of insulin spread over the first three hours of treatment; and we administer as a routine 2 g. of potassium chloride every two hours as soon as the patient can swallow, provided urine is being excreted freely. Perhaps it is this latter measure which has done more than anything else to improve our mortality figures in diabetic coma during the last few years, for, as the result of the insulin therapy and the treatment of the dehydration, potassium passes from the extracellular to the intracellular fluids and the serum potassium may fall to extremely low levels. Thus death from hypopotassaemia may occur during the recovery phase from diabetic coma

in spite of the fact that the ketosis and hyperglycaemia have been adequately controlled. I used to think it very unfair that so many of my patients died when I had apparently cured them as judged by the restoration of their blood glucose concentrations to normal and the disappearance of ketosis from their urine and breath.

I could go on for a long time with reflections on our changing attitudes to diabetic problems in comparison to what they were in the early days: there is the greater emphasis on the role of diabetic neuropathy in the causation of trophic lesions on the feet of diabetics, and the realisation that many of the ulcers which we used to think were entirely due to gangrene are really the result of a mixture of angiopathy and neuropathy; the carbohydrate feeds traditionally given to diabetics immediately prior to surgical operations so frequently caused aspiration pneumonia that if it is necessary to give pre-operative glucose at all it is now always given intravenously; the foetal loss rate in diabetic pregnancies which was over 50 per cent. twenty-five years ago has now been reduced to 20 per cent., chiefly by insisting on a Caesarean delivery about the thirty-sixth week; there are all the new insulins, though it may be doubted if globin insulin and the insulin suspensions really represent any very important therapeutic advance over soluble insulin and zinc protamine insulin except for a few cases; and finally there are the exciting new possibilities which arise with the discovery of the oral hypoglycaemic agents, though British medicine is to be congratulated that its approach to these new remedies has been one of conservative caution until their proper place in therapeutics (and it seems at present to be a limited one) has been clarified by long term clinical trials. One could elaborate at length on these and many more changes in diabetic practice, but your editor has wisely imposed some limits on my verbosity.

INTERRUPTED FERTILITY

COLLECTED FROM THE SOCIETY'S ARCHIVES BY C. VAUGHAN RUCKLEY

From "A case by Dr. TAYLOR.....1777."

Mrs Buff, wife of Mr Buff, silk weaver in Fashion Street in Spitalfields, London, aged twenty-seven years, the mother of several Childrine, on 27th of July 1774, having gone her usual time of pregnancy, was attended by her midwife several days, but tne labour pains ceasing, the midwife left her promising to return soon, but did not fulfill her promise, Mrs B. not being delivered of her child, thought she might have a month longer to go & went about her domestic affairs as usual, Xmas following she prov'd with child again & not being delivered of the former one she became uncommonly big and unwieldy, she applyd to several physicians for advice & particularly to Dr. Wyman an eminent man midwife in Aldermanbury, who ordered her a variety of purgative medicines but without relief, in June she sent for me, and after hearing the above narrative I assured her of being with child, & in October following I laid her of a healthy living child, having had an easy natural labour, she recovered very well until the 10th day, she was taken of a violent purging, her stools very offensive and of a dark bloody appearance, having taken some astringent medicines with Diascordium the Diarrhoea ceas'd but was followed by profuse sweats which weakened her considerably & she was obliged to wean the child I had laid her of, the sweats and purging stools having her for 3 months, she was much reduced in her strength, about this time the thigh bone of a child came away in a purging bloody stool. a few days after half a frontis, two months after she passed half of the under jaw having the sockets of five teeth well marked, all these bones were of a brown darkish colour & were voided with purging bloody stools. March 5th a ragged piece of upper jaw came away, she

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Some Aspects of Nutritional and Toxic Liver Injury

Based upon a Dissertation on "Hepatic Cirrhosis" given before the Society on Friday, 31st January 1958.

By A. W. DELLIPIANI

The problem of nutritional liver damage and cirrhosis has been made easier and at the same time more difficult as a result of animal experiments and attempts to apply them to man. The clinical syndromes of nutritional liver injury are best classified according to the method of Sherlock:

1. The Tropical and Subtropical Clinical Syndromes—The Kwashiorkor Syndrome.
2. Alcoholic Liver Injury.
3. Liver Injury caused by Protein Deficiency secondary to other disease.

The experiments carried out on rats in the field of nutritional liver damage are well known. For this reason, and also because their aetiological relationship to dietary liver injury in man seems to be limited, a brief resumé of these will suffice.

It has been found that essentially two types of nutritional injury can be caused in the rat—

(*a*) Fatty infiltration—This is of centrilobular distribution and is the result of lack of choline and its precursors, the so-called lipotropic substances.

(*b*) Acute liver atrophy—This is the result of feeding diets low in sulphur containing amino-acids and especially cystine.

The first of these, if of sufficient severity, progresses to a Laennec cirrhosis, whilst the latter, if the animal survives, gives rise to post-necrotic scarring. Protein protects against these lesions and methionine, because of its content of labile methyl groups, plays an important dual role.

How are these findings to be applied to man? Let it be said straight away that there is no evidence that in man dietary deficiency is ever a direct cause of post-necrotic scarring subsequent to acute yellow atrophy. That it might be a conditioning factor has been suggested, especially by Himsworth and Glynn, in such conditions as the acute or sub-acute necrosis of pregnancy or in poisoning. This aspect will be discussed later, but firstly the relationship between fatty infiltration in animals and the kwashiorkor syndrome will be considered.

Many varieties of this syndrome have been described. These depend on factors superimposed on the basic syndrome, such as iron in the siderotic cirrhosis of South Africa, the hepatotoxic alkaloid senecio in senecio poisoning in the same region, and also possibly in veno-occlusive disease in the West Indies, and the effects of fruits such as the ackee in the vomiting sickness of Jamaica.

A fatty liver is characteristic of kwashiorkor but one of the striking features is that, unlike the nutritional lesions in animals, it is histologically of portal distribution. However, the fact that in man a fatty liver does result from protein deficiency provides an encouraging analogy with animal findings. Rigorous proof of the association between protein deficiency and fatty infiltration in man is, however, difficult to obtain. Moreover, it would seem that fatty liver is not necessarily the most important lesion in

kwashiorkor, since the degree of infiltration seems to bear little relation to the severity of the disease. Again though the syndrome will respond to an improved diet, and especially milk, there is no clearcut evidence that choline or methionine will improve or even arrest the established condition. Thus the cause of fatty liver in man does not seem to be deficiency of the known lipotropic substances that affects the rat. The different zonal distribution of fat would seem to emphasise this and recently several groups of workers in the U.S.A., Canada, and India have succeeded in producing fatty infiltration in the rat liver which, as in man, is also perilobular. This was done using low protein diets and shows that although deficiency of this substance can indeed promote excessive deposition of fat in the liver, the mechanism by which it occurs is unknown.

A new approach to the problem introducing the humoral element has been prompted by observations on the altered pancreatic secretions which are known to occur in kwashiorkor. In a recent paper Gillman and Gilbert are impressed by the rapidity of onset of the fatty liver in the disease which leads them to suspect hormonal imbalance as responsible for the changes. In the baboon the development of the lesion seems to be dependent on a dynamic equilibrium between adrenocortical steroids, insulin, and thyroxine. In the absence of the pituitary, the administration of cortisone will promote the development of fatty livers in these animals provided that insulin is inadequate; excessive thyroxine increases the fatty deposition. The lesions are similar to those seen in kwashiorkor. Though much has still to come from this line of research, dietary influences are known to have a marked effect on human endocrine secretions, and such factors might well be of importance in promoting fatty deposition in a liver already suffering from protein lack, even though the signs of this may not be histologically detectable. Many writers are nowadays of the opinion that the primary change in kwashiorkor may well be in the pancreas.

Another problem is the relationship of the nutritional and the cirrhotic liver, and one would nowadays question the long accepted view that the one leads to the other. Though this is true of the experimental animal, Dible has pointed out that, if the same factors were to apply to man, more fat than is actually ever found in man's liver would have to act over a longer period of time than is actually the case. Thus, though the fibrous tissue might be a replacement fibrosis of cells killed by fat, as Hartroft showed in animals, it might also be that the fatty change found in such a liver is rather the result of disordered metabolism than the cause of the events which eventually lead to cell necrosis and subsequent cirrhosis.

Geographically there is, it is true, fairly close association between the incidence of kwashiorkor and Laennec's cirrhosis. Nevertheless in Brazil where fatty livers were until recently prevalent, the incidence of cirrhosis is low and the reverse is true in the Gambia. No one, it must be noted, has yet succeeded in showing a natural progression of fatty liver to cirrhosis by liver biopsy technique. In addition it must be remembered that though kwashiorkor is a childhood illness, cirrhosis is an adult one, and that though the incidence of kwashiorkor is equally distributed amongst the sexes, cirrhosis is five times commoner in the male. Though there might be some protective factor in the female the higher incidence of virus hepatitis in women, often with complicating massive necrosis in pregnancy, would, as Edington has pointed out, almost make one expect a higher incidence of cirrhosis in the adult female. In the three countries where true cirrhosis has been found to occur commonly in children—Jamaica, India, and the Gambia, in no case does the process seem to begin with fatty infiltration, and the stellate portal fibrosis which is often seen in kwashiorkor and which

many would consider the precursor of portal cirrhosis, has been seen in the absence of kwashiorkor, and indeed in the absence of fat. Dare one possibly suggest, therefore, that rather than the result of fatty change, cirrhosis itself is also a direct manifestation of alterations in the rhythm of the endocrine orchestra? However, in spite of these comments many would still favour the cause and effect association of fatty change and cirrhosis.

Nothing will be said about the third group in Sherlock's classification of aetiological factors in cirrhosis since, though liver changes are described in diseases involving primary pancreatic deficiency, ulcerative colitis and in such rare metabolic disturbances as the De Toni-Fanconi syndrome, extreme liver changes going on to cirrhosis are rare.

A note on the relationship of alcoholism and chronic liver change, a topic of much general interest, is more appropriate. One must accept that there is an association between the two. Sherlock quotes an 18 per cent. incidence of cirrhosis in alcoholics and the figures are said to be higher in America. If one accepts the association one must either postulate a direct effect by this drug, an indirect one via a nutritional mechanism, or even a combination of both. In favour of the first approach one recalls the disastrous effects which alcohol may have in a patient convalescing from infective hepatitis, or the precipitation of hepatic coma in a patient with cirrhosis.

It is well to recall at this point the experiments of Best and his associates carried out in 1949. As a result of very carefully controlled work, they concluded that there is no more evidence of a specific toxic effect for pure alcohol than there is for sugar. This conclusion was based on the observation that dietary supplements of sucrose given to rats on basal diets caused hepatic lesions identical to those caused by an isocaloric amount of alcohol. These results suggest than an imbalance between caloric intake and the supply of relative food factors is the cause of the hepatic lesions. There is, in other words, a relative lack of lipotropic agents. As has already been mentioned, these substances might not be of the same importance in man, but there is little reason not to suppose that a relative protein deficiency produced by alcohol in man might well condition a fatty liver going on to cirrhosis—that is if this latter association is accepted.

However, if the harmful effects of alcohol were due solely to the increased caloric intake then they should be abolished by restricting calories. When this is done in rats, one group of which is given alcohol and the other sucrose, the alcoholic rats show more advanced liver lesions than the sucrose fed animals. Thus Best's experiments do not tell the whole story.

One cannot therefore rule out a direct toxic effect by alcohol though it would seem that this is probably small and not as important as the relative protein deficiency induced by the substance. A true protein deficiency is often an additional factor since its cost makes it a luxury. Chronic gastritis and pancreatitis may produce a vicious circle. Alcoholics often show the signs of general dietary deficiency and on the whole alcoholic portal cirrhosis falls into place alongside pellagra, beri-beri, and Wernicke's encephalopathy as a dietary deficiency conditioned by chronic alcoholism.

Even more interesting than nutritional liver damage, and not entirely unassociated with it, is the problem of toxic liver injury. The importance of this as a causative factor in cirrhosis has probably been exaggerated in the past. Himsworth, subsequent to animal observations, divided the hepatotoxic agents into two groups. The first contains those which produce zonal necrosis and the other those agents which produce massive necrosis conditioned by dietary deficiency.

1. *Producing Zonal Necrosis.*
   (*a*) Chemicals—Industrial carbon tetrachloride, chloroform, phosphorus, and tannic acid.
   (*b*) Intoxications—e.g. Eclampsia.
   (*c*) Infections—The yellow fever, I.H. and S.H. viruses.
2. *Producing Conditioned Massive Necrosis.*
   (*a*) Industrial Chemicals—Trinitrophenol, dinitrophenol, dinitrobenzol, trinitrotoluol, tetrachloroethane.
   (*b*) Drugs—Cincophen, plasmoquin, mepacrine.
   (*c*) Toxic Grain—Selenium poisoning.

Taking this classification in conjunction with the pathology makes it unlikely that toxic liver injury should be a common cause of cirrhosis.

The characteristic finding in the first group is the tendency for the reticulum to remain patent so that even in severe zonal degeneration cirrhosis does not occur, recovery being complete in about two weeks in animals. This is due partly to the maintained reticulum, the preservation of the blood supply and the zonal distribution of the lesion which leaves a sufficiently large number of cells in the lobule to permit regeneration. Repeated doses of the irritant acting at intervals which are so short that they impose a new lesion on one which is not yet healed, however, result in a fine and typically uniform fibrosis. At this point it must be stressed that Himsworth believes that zonal necrosis is a pure lesion because all the evidence suggests that massive necrosis is not a severe and fulminating variety of the zonal type.

This introduces the importance, if any, of virus hepatitis as a causative factor of cirrhosis. This has been discussed often and at length with the object of trying to fill the gap in the aetiological classification of the cirrhoses. In this country where diet and alcohol play but a minor role in the aetiology of chronic hepatitis, it would be not only convenient, but also of considerable satisfaction to explain away most of the cryptogenic group as post-hepatitic. Ratnoff and Patek and Sherlock give figures of 6·5 per cent. and 33 per cent. respectively for the incidence of a history of previous jaundice in their groups of cirrhotic patients. In the same group Sherlock found that 49 per cent. of the patients gave no history which might indicate an obvious aetiology. The cryptogenic group is indeed large. It has, however, been pointed out that in an epidemic of virus hepatitis, a large number of cases occur in which jaundice is not manifested and which are difficult or impossible to recognise clinically. Needle biopsy studies reveal that in these subjects obvious lesions occur and that these cases may take as long, if not longer, to recover complete good health as those in which jaundice is great. One is therefore tempted to suggest that a non-icteric lesion might rarely lead to cirrhosis.

Looking at the pathology more closely, the human lesion is typical of the zonal type which Himsworth observed in animals. Mild cases show a predominantly central zonal lesion by liver biopsy technique, whilst in severer cases the lesion is more extensive but still zonal, the incidence of acute yellow atrophy being rare. The fascinating tendency for a maintained reticulum is marked and recovery, which is complete, is said to be the rule in 99·8 per cent. of cases.

In those cases where cirrhosis supervenes, the mechanism might be, as Himsworth suggests, repeated attacks of hepatitis before healing from a previous attack has been completed, this resulting in a disorganised reticulum with subsequent fibrosis. In any zonal lesions its exact distribution, whether mid, central or peripheral zonal, is a mystery though the presence of definite vascular territories has been suggested as an explanation.

Though fibrosis might depend on the original zonal location, it would seem impossible to forecast which part of a regenerating nodule would be most vulnerable to the repeated destructive action of the same irritant and hence where fibrosis might begin. Eventually, however, the picture would be indistinguishable from that of the typical Laennec cirrhosis.

This, however, is not the whole story, and many pathologists would prefer to believe that post-hepatitis cirrhosis is really the result of acute yellow atrophy, and that the post-necrotic scarring which results eventually becomes histologically indistinguishable from the classical Laennec type, via progressive fibrosis and contraction of fibrous bands. There is little doubt that as a result of the regeneration and fibrosis which constitute post-necrotic scarring, there is a tendency for freer communication between the hepatic and portal veins than exists in the normal liver, this change occurring especially at the periphery of the regenerating nodules and in the fibrous septa. The portal blood is therefore shunted past the nodules which come to rely more and more on the arterial supply. There is therefore likely to be further necrosis, a diminution in the size of the nodules, a rearrangement so as to provide a more favourable distribution of blood supply, and, in general, a maintenance of the cirrhotic process which will tend to alter the picture of post-necrotic scarring through time to one approximating to that of the Laennec variety. This would explain the variability in size of the nodules and in the width of the fibrous bands which is sometimes seen in post-hepatitis cirrhosis and which would seem to indicate that the cirrhosis had its origin as a post-necrotic scarring.

One is therefore left with the possibility that post-hepatitis cirrhosis is: (*a*) the result of organised sub-acute liver atrophy, or (*b*) the result of repeated attacks of zonal necrosis.

That a non-icteric attack of hepatitis might give rise to cirrhosis is of course inconsistent with the first view, but not unlikely if the second is accepted. Sherlock seems to be in favour of the first view, but also points out that even in a zonal lesion where there is much centrilobular loss of liver cells, there is condensation of reticulum. This might conceivably go on to cirrhosis and is a convenient way of steering between the above groups. The problem is therefore involved, and one might further suggest that there is no reason why both methods should not operate in the causation of post-viral cirrhosis. Dible does in fact suggest that a massive necrosis is merely a farther step in the process of zonal necrosis. As has been mentioned, however, Himsworth prefers to believe that each lesion is one in its own right and that when massive necrosis occurs in man, it is a lesion conditioned by nutritional factors. This introduces the second group of substances in Himsworth's classification. (See Table.)

There is some evidence that these substances produce their lesion when conditions are rendered suitable by dietary deficiency. Thus though 25 per cent. of industrial workers exposed to TNT develop symptoms other than in the liver, only 0·2 per cent. develop acute yellow atrophy, and a nutritional basis is the most likely. In animals there is some evidence that this substance acts by raising the B.M.R. thus possibly outrunning the liver's demand for cystine. Similarly it is suggested that selenium produces its toxic effects by replacing sulphur in cystine which is rendered unavailable. There is of course the danger of applying these results from animals too dogmatically to man without sufficient direct evidence. However, whatever the mechanism, if such a view as to the aetiology of massive necrosis in man is correct in respect to chemical agents, it is tempting and perhaps not totally unjustified to apply the same to infective agents. Thus pregnant women seem particularly liable to develop massive necrosis subsequent to virus hepatitis.

Although it is true that cases have been described in which recovery from the disease has been noted in spite of proteinaemia and although massive necrosis has been observed in well nourished people, it is difficult to refute the evidence of the occurrence of that complication in Denmark during the late war years, or in central Europe between 1915-20, as not indicative of a predisposing nutritional element.

Before ending this article, the probable importance of multiple factors operating in the causation of hepatic injury must be emphasised. Himsworth is of course the protagonist of this view and it has been brought to the fore recently by Waterlow and Bras. In the animal liver, at least, nutrition is important in determining the susceptibility of the organ to the effects of irritants. Waterlow and Bras stress the fact that the liver may show no histological evidence of this in the early stages. Thus in animals, even before fat appears in the cells, there occurs a loss of several cytoplasmic constituents, protein, phospholipids and ribonucleic acids as a result of protein-deficient diets. This must involve some compromising loss of liver enzymes. There is no reason why this should not apply to man also. Thought along these lines has led to the recent revival of the concept that malaria might after all be a cause of cirrhosis, in the Gambia for example, where cirrhotic livers are found in children in the presence of malnourishment though fatty livers are uncommon.

Thus it seems that toxins and infections, whether bacterial, viral or parasitic, or even, as we have seen more recently, humoral agents, when combined with malnutrition might play an important role in the causation of chronic liver damage, but there is still much to be learnt about the pathogenesis.

Lithograph by Schenck after a drawing by J. Archer
By courtesy of The Wellcome Historical Medical Museum

SIR JAMES YOUNG SIMPSON

By WILLIAM L. FORD

"He is the flower (such as it is) of our civilisation and when that stage of man is done with, and only remembered to be marvelled at in history, he will be thought to have shared as little as any in the defects of the period, and most notably exhibited the virtues of the race."

(From Preface to *Underwoods* by Robert Louis Stevenson)

Among the many eminent men who have been Members or Honorary Fellows of the Royal Medical Society a number have attained a place in world history; one such is Sir James Y. Simpson—physician, teacher, discoverer and philanthropist.

Most of us associate his name with the introduction of chloroform anaesthesia, and indeed seldom can a major advance in applied science have owed so much to one man; yet the story of Simpson's life and deeds is so remarkable that, had he never discovered anything, he would still be remembered as a great man.

Dr Simpson joined the Society after graduating M.D. in 1832 at 21 years of age. Three years of active participation in the Society culminated in his election to the office of Senior President. A writer in *The Scotsman* some years later describes a visit to the Society at this time:

"The Presidentship of such a Society is naturally an object of laudable ambition for every advanced student or young practitioner and many of the most illustrious names that have adorned Science or Medicine have recorded their elevation to that post as among their earlier honours. On the evening referred to, the Chair was occupied by a young man whose appearance was striking and peculiar. As we entered the room his head was bent down to enable him, in his elevated position, to converse with someone on the floor of the apartment, and little was seen but a mass of long, tangled hair, partially concealing what appeared to be a head of a very large size. He raised his head and his countenance at once impressed us. A poet has described him as one of 'leonine aspect.' Not such do we remember him. A pale, large, rather flattish face, massive, brent brows, from under which shone eyes now piercing as it were to your inmost soul,

now melting into almost feminine tenderness, a coarseish nose, with dilated nostrils, a finely-chiselled mouth, which seemed the most expressive feature of his face, and capable of being made at will the exponent of every passion and emotion. Who could describe that smile? When even the sun has tried it, he has failed, and yet who can recall these features and not realise it as it played round the delicate lines of the upper lip, where firmness was strangely blended with other and apparently opposing qualities? Then his peculiar, rounded, soft body and limbs, as if he had retained the infantile form in adolescence, presented a *tout ensemble* which, even had we never seen it again, would have remained indelibly impressed on our memory. 'You are in luck to-night,' said our conductor, 'Simpson is President.'"

Simpson had already begun to interest himself particularly in obstetrical medicine and he delivered the Presidential dissertation on "Diseases of the Placenta." To this he devoted a prodigious amount of work. For one night he went without sleep altogether; for many others he was in bed for only three or four hours. Simpson was thoroughly conditioned into the habits of hard work, for he entered the Faculty of Arts when only fourteen, and was supported for several years by the generosity of his older brothers.

To our knowledge this dissertation represented the first attempt in Britain to discuss placental disease. As Simpson pointed out in his opening remarks, the works of the great obstetricians, Smellie, Denman, Ramsbotham and others, contain no more than occasional observations on placental conditions. His references include many continental authors, chiefly French and German.

The great importance of this previously neglected organ is emphasised from the beginning and stress is laid on the need for careful observation and investigation. The author then proceeds, in fourteen thousand words, to give evidence of his own erudition and personal observation.

The bulk of the dissertation discusses firstly placental congestion and haemorrhage, and secondly inflammation or placentitis. It was not realised until many years later that what were thought to be chronic abscesses described by accoucheurs as "scirrhous of the placenta" were in fact areas of infarction. Despite this error in pathology, Simpson's clinical observations are as valid now as then; likewise his catalogue of causes—"Trauma, violent succussions, sudden movements, frights, emotions, all kinds of lively and profound sensations, and diseases of the mother."

A brief, lucid survey of other, less common, diseases of the placenta completes the dissertation.

The reading of this work must have taken nigh on two hours. Simpson concludes with an apology for its "great length and its great imperfections." We may concede the former, not so readily the latter. Indeed the dissertation was an outstanding success, and attracted widespread attention—mostly outside Edinburgh, however. Later it was translated into French, German and Italian.

Six years later came the climax of Simpson's academic achievement; he was elected to the Chair of Midwifery, at the age of 29, in the pursuit of which he overcame crippling disadvantages and bigoted opposition. Characteristically, he put his whole heart into obtaining the vacant chair —a goal which he had set himself at his graduation. No stone was left unturned in presenting his case to the University or in soliciting testimonials from his many acquaintances. At one sitting he wrote for more than seventy consecutive hours and, all in all, the campaign cost him almost two years' salary. His intellectual prowess was unquestionable but three factors were held against him—his youth, his humble birth (he was a "poor baker's son" from Bathgate), and his unmarried state. The first two of these were not in his power to alter, but a few weeks before the election he married a

distant cousin, rather sooner than he felt was justified by his economic circumstances. On the eve of his election he was very pessimistic about the outcome, and his pessimism was fully justified according to those who were best informed. The result was against all expectations and at that time few could have realised that it heralded such a brilliant phase in Edinburgh medicine.

His erudition and charm as a teacher, and kindly disposition and indisputable competence as a physician, caused the reputation of Simpson to grow and spread far beyond the city to which he gave his life. He had always abhorred human suffering, and had nearly abandoned medicine as a student, on witnessing the amputation of the breast on a poor Highland woman. Before becoming Professor the idea of painless operations was firmly established in his mind. He experimented with mesmerism with occasional success. However, in 1846, news came from America of the first trials of ether; this was enthusiastically welcomed by Simpson who quickly carried out experiments of his own design and was the first to use this anaesthetic on women in childbirth.

Simpson was so obsessed with ether that, for a time, he could think of nothing else. But he was not blind to its imperfections—the large quantity of it which was often required; the slowness of induction; its unpleasant, penetrating smell and its tendency to cause bronchial irritation. Without delay he set about trying to discover a substitute with fewer undesirable properties. He tested several volatile organic materials, always using himself as the experimental animal. Early in 1847 he inhaled from a tumbler the then rare "perchloride of formyle"—chloroform—which had been identified chemically fifteen years earlier by Soubeiran and Liebig. So rapidly did he become unconscious, that he straightaway arranged a more elaborate trial with his assistants Keith and Duncan. Again the effects were spectacular, and Simpson's first words when he awoke were "This is far stronger and better than ether."

Three operations were performed under chloroform at the Royal Infirmary and an epoch-making pamphlet on the unblemished success of chloroform published. It bore a motto from Bacon—"I esteem it the office of a Physician not only to restore health but to mitigate pain and dolours."

However, very few of Simpson's eminent associates in medicine were of anything approaching this opinion. Ceaseless vituperation and accusasions of personal ineptitude were hurled upon his head. Simpson was faced with the fight of his life. He might have given up embittered, but he persevered. He fought bravely and he won.

Some of the arguments against chloroform, that it would interfere with other forms of treatment, and that it would lead to insanity might be produced to-day against the introduction of any new drug. But what could never be advanced to-day was the hysterical laudation of extreme and prolonged agonies. Suffering was held to be the best of tonics. Before Simpson's time surgery was a horrid trade; a sordid, almost sinister side of human affairs. Yet those who had to administer the tortures, not to bear them, were satisfied enough. All except Simpson. Through anaesthesia the cruel knife has become the healing knife. Although he was certainly abreast of his time in science, he was a century ahead of his time in human values. For a mere 12,000 years, man has lived as a "civilised" creature, and civilised behaviour is not really deeply imbued in human nature. To-day we possess, as part of our culture, a certain amount of social conscience, and should we be magically transported back a hundred years, to a period which we often associate with gracious and elegant living, what

would surprise us most of all, and indeed terrify us, would be the callous acceptance of avoidable human suffering and misfortune.

This is illustrated in a letter to Simpson from Dr. George Wilson who signed himself "An Old Patient." As a telling vindication of chloroform it strongly bolstered Simpson's cause. Dr. Wilson recalls an experience two or three years before the introduction of chloroform:

"During the operation, in spite of the pain it occasioned, my senses were preternaturally acute, as I have been told they generally are in patients in such circumstances. I watched all that the surgeons did with a fascinated intensity. I still recall with unwelcome vividness the spreading out of the instruments, the twisting of the tourniquet, the first incision, the fingering of the sawed bone, the sponge pressed on the flap, the tying of the blood vessels, the stitching of the skin, and the bloody dismembered limb lying on the floor.

Of the agony it occasioned, I will say nothing. Suffering so great as I underwent cannot be expressed in words, and this fortunately cannot be recalled. The particular pangs are now forgotten; but the black whirlwind of emotion, the horror of great darkness, and the sense of desertion by God and man, bordering close upon despair, which swept through my mind and overwhelmed my heart, I can never forget, however gladly I would do so. Only the wish to save others some of my sufferings, makes me deliberately recall and confess the anguish and humiliation of such a personal experience; nor can I find language more sober or familiar than that I have used to express feelings which, happily for us all, are too rare as matters of general experience to have been shaped into household words.

Those are not pleasant remembrances. For a long time they haunted me, and even now they are easily resuscitated; and though they cannot bring back the suffering attending the events which gave them a place in my memory, they can occasion a suffering of their own, and be a cause of a disquiet which favours neither mental nor bodily health. From memories of this kind, those subjects of operations who receive chloroform are of course free; and could I, even now, by some Lethean draught erase the remembrances I speak of, I would drink it, for they are easily brought back, and they are never welcome."

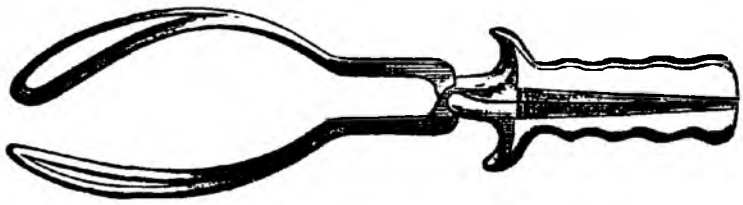
The sales of chloroform snowballed from 1850; familiarity vanquished fear, and in 1853 Queen Victoria insisted on having chloroform administered during the birth of her eighth child, Prince Leopold, Duke of Albany.

Simpson's achievement brought him world-wide fame and unaccustomed prosperity. The city and the University shone in the light of his reflected glory.

Although chloroform anaesthesia was the climax of his life's work, his restless genius was productive to the end. In 1859 he perfected and introduced acupressure—a method of haemostasis by which bleeding vessels are compressed between a long needle, which is later removed, and solid tissues. Previously the ligatures used in surgery invariably gave rise to sepsis. Acupressure was first adopted in Aberdeen and spread throughout the world. The Edinburgh surgeons, led by the amazing Professor Syme, violently resented what they considered an intrusion into their private field. Whilst delivering a lecture, Syme tore up Simpson's pamphlet answering objections to acupressure without a single argument against it—a demonstration that his opposition was governed by emotion and not by reason. As it became universally adopted, acupressure saved many lives until it was superseded by the introduction of antiseptic techniques and superior ligatures.

In Simpson's day quantitative arguments were seldom applied to medical

problems. However, in several investigations he went to great lengths to collect results from far and wide and to draw rational conclusions from them. In the early days of chloroform it was suggested that the drug had been responsible for a number of deaths; Simpson showed that not only did chloroform avoid indescribable agony but by doing so it clearly saved lives. In the last twenty years of his life he devoted much energy to the problem of the high mortality of surgical cases in city hospitals. He produced several papers on the subject, and in one investigation of over 4000 cases showed that death followed amputation of a limb four times more



SIMPSON'S LONG FORCEPS

From Johnstone and Kellar's *Text-book of Midwifery*
by courtesy of Messrs A. & C. Black.

frequently in the large city hospitals than in the smaller country hospitals. He strongly advocated hospital reform on the lines of small, well ventilated hospital units preferably sited in the country. Lister showed us why overcrowded hospitals were so sinister but until his theories were accepted Simpson's work was a telling force for the better.

In all his enterprises Simpson had laboured in the midst of controversy. Many men are controversialists by choice but he must have hated it all. He was a man of peace and benevolence but his inexorable honesty never allowed him to compromise with the many (like Syme) whose intellectual genius was unmatched by moral vision. Moreover, forgiveness was never withheld from the most bitter adversary.

The legend of the "lad o' pairts" is beautifully exemplified by Simpson. He rose from extremes of poverty and obscurity not by shrewdness nor by popularity nor by fortune's favour, but entirely by honest, hard work and a marvellous ability.

The transcendent feature of Simpson's personality was his overwhelming compassion for any human being in agony or distress. For him to be kind was a necessity. He knew himself great pain and frequent grief. As a youth he endured migraine and during his last years angina was his constant companion. He was orphaned when still a child, and of his beloved family of nine, five predeceased him.

He had a simple faith in Christian teaching and a deep love of his native land—"That most sweet of all sweet countries, old Scotland"—as he put it.

It might be thought that the baronetcy conferred in 1866 was one of the highlights of Simpson's career. In fact he hardly noticed it. His deeds alone ennobled him and he preferred his reward in the gratitude of his patients. When he died in 1870, aged 58, burial in Westminster Abbey was offered, and declined by his family. He had chosen to rest in Edinburgh. Thirty thousand people from all classes and of every age attended the funeral procession. It is said to have been the largest and most moving the city has ever known.

THE AETIOLOGY OF DISSEMINATED SCLEROSIS

Based upon a Dissertation on "Disseminated Sclerosis" given before the Society on Friday, 10th January 1958.

By J. G. TURNBULL

> Le prognostic jusqu'ici est des plus sombres. En sera-t-il toujours du même? On peut espérer que lorsque la maladie sera mieux connu, le medicin apprenda à tirer parti de ces tendances spontanées aux rémissions que se trouvent signalées dans un bon nombre de ces personnes. Charcot. 1865.

Disseminated sclerosis is the commonest nervous disease in this country; in the north of Britain at least one in 1300 adults is affected. If any rational or successful therapy is to be introduced the cause must be found and I therefore propose briefly to discuss the main theories of its aetiology.

Disseminated sclerosis is one of the primary demyelinating diseases (as opposed to those causing secondary demyelination such as infarcts) which can be defined as "diseases of the central nervous system showing destruction of myelin sheaths with relative sparing of axon cylinders and supportive tissues usually occurring in multiple foci."

The main theories of aetiology are:—

(1) The Strumpell-Muller hypothesis of dysplastic glial development.
(2) Infective theories.
(3) Biochemical and chemical theories.
(4) Vascular theories.
(5) Allergic theories.

Also various precipitating and aggravating factors such as climate, geography, trauma and infection, can be twisted and turned to fit most of the above theories.

The Strumpell-Muller theory arose from a mistaken concept of the pathogenesis of disseminated sclerosis, namely that the astrocytic overgrowth and occurrence of atypical monster astrocytes, seen otherwise in the malignant glioma, were evidence of a neoplastic process. However, in the earliest lesions astrocytes are not abundant and workers now agree that demyelination or loss of the satellite oligodendroglia is the first change. Oligodendroglia are absent even in the earliest lesion, and studies have shown that, when viable, their processes encircle the myelin sheaths like ribbons and it is likely that the integrity of the myelin depends to a great extent on these cells. They are the most sensitive cells in the C.N.S. and for this reason I would like to introduce the concept that the disappearance of these cells and perhaps therefore demyelination is the response to the least noxious agent able to harm the C.N.S. Indeed all the demyelinating diseases could then be considered as steps up the scale of destruction due to a variation in one of many possible factors, and it is interesting to note that in very acute disseminated sclerosis softening and liquefaction have occurred.

The infective theories arose from the occurrence of "epidemics" of disseminated sclerosis in different localities though many other factors such as those mentioned above could play a part. Indeed there is little clinical evidence that contact or similar factors are involved. Pathologically the lesion is not typical of infection; the perivascular cuff, absent in the early lesion, is probably a response to degeneration rather than to an organism.

The infective agents incriminated fall into three groups:

(*a*) An exogenous organism might secrete a myelinolytic toxin acting via the circulation. Many bacterial toxins can cause experimental demyelination but attempts to incriminate any have repeatedly failed. It is interesting to note here that a high incidence of unsuspected sinus infections are uncovered at autopsy.

(*b*) Older workers, including Steiner, thought that disseminated sclerosis was an atypical form of syphilis and the apparent response to arsenicals strengthened this theory. Steiner claimed to have found spirochaetes and silver staining débris in the C.S.F. at autopsy in disseminated sclerosis patients. Various claims for culture of these organisms were made at this time. Rabbits injected with C.S.F. of patients developed symptoms and lesions more similar to acute disseminated encephalomyelitis than disseminated sclerosis; both spirochaetes and silver staining débris were found at autopsy. However, better controlled experiments showed the organisms occurring in the control group as well, and these organisms were later proved to be normally present in rabbits. Why then did the previous animals show demyelination and why were spirochaetes found in human subjects? The answers to these questions are perhaps that the disease might be due to allergy or a virus in the rabbits and the organisms found in human beings might be a manifestation of post-mortem organismal dissemination analagous to that of *B. Coli* or *Cl. welchii*. The last word on this subject came from Ichelson in America, who claims to have cultured spirochaetes similar to Steiner's organisms from the C.S.F. in a high percentage of a large group of disseminated sclerosis patients and in none of a control group. Imunological evidence was also cited.

A virus has, of course, been suspected as the cause of disseminated sclerosis and not all work on this has been negative. In 1930 Chevassut stated that she had cultured a virus which she called Spherula Insula, from the C.S.F. of a high percentage of disseminated sclerosis patients and from none of a control series. Animal innoculation was inconclusive and though she claimed that a therapeutic vaccine gave clinical improvement and that the sera from vaccinated patients inhibited the growth of the spherula, her work has since been discredited.

In 1946 Margoulis compared acute disseminated encephalomyelitis (A.D.E.) with disseminated sclerosis clinically, pathologically and experimentally and noted the following points:

(*a*) The occasional clinical transition of A.D.E. to disseminated sclerosis.

(*b*) The pathological differences were merely an expression of acuteness or chronicity of the lesions.

(*c*) The isolation of a virus from the C.S.F. of A.D.E. patients and its neutralisation by the sera of fifty per cent. of a group of disseminated sclerosis patients and seventy per cent. of A.D.E. patients.

(*d*) Vacine therapy giving apparent improvement in disseminated sclerosis patients.

A more critical investigation published only this year discredits the above.

Perhaps it is appropriate to say here that all workers claim some improvement for therapies based on their ideas of the aetiology.

Before leaving the infective theories it should be pointed out that the hypothetical organism need not liberate a demyelinating toxin or cause demyelination itself as the demyelination might be due to the endogenous release of a myelinolytic agent in response to some organismal irritation.

Therefore the various theories still to be discussed do not necessarily contradict the above.

Many chemical agents such as carbon monoxide, bacterial toxins, and sodium taurocholate cause demyelination, but the most studied is cyanide. Variation in the size and frequency of doses given to animals caused lesions from acute cortical necrosis to chronic demyelination. Massive doses produced liquefaction and death, medium doses caused a picture akin to A.D.E., and small doses led to lesions like disseminated sclerosis. It has been suggested that while the large doses affect their high immediate oxygen requirements, the neurones are able to resist the small repeated doses because of their adequate oxidative enzyme systems and circulation.

Marburg postulated that a circulating lipase might produce the demyelination and produced this possibility in vitro. He claimed to have observed raised lipase levels in the urine of disseminated sclerosis patients and advanced liver or pancreatic disease as the possible cause. Although later work failed to confirm this, a lipase might be produced locally from cellular ferments and if this were so, it would be "used up" locally and it is unlikely that much would reach the general circulation. Along similar lines Lumsden thinks that the enzymes for manufacture and breakdown of myelin might exist side by side in the oligodendroglia and an imbalance in these might be the cause.

Could disseminated sclerosis be a deficiency disorder like pernicious anaemia or a heavy metal poisoning? Campbell in 1947 reported that four out of seven scientists working on swayback "contracted" disseminated sclerosis, and though other factors may be involved this incidence is striking. Swayback is a disease of lambs born in certain areas and it is characterised by low copper levels both in the ewe and in the lamb; the pasture is not deficient in copper. Pathologically it resembles another human demyelinating disease called Schilder's disease. High lead levels have been found in areas with swayback and in areas with disseminated sclerosis, but this relationship is by no means constant for either. Swayback notoriously occurs in highly limed areas. If a swayback producing ewe is taken to a non-swayback area and even fed on a low copper diet she does not produce swayback lambs. Obviously something in the pasture has interfered with the absorption or metabolism of copper. We can postulate (*a*) high lead levels preventing absorption of copper, (*b*) a virus acting in the presence of, or causing, copper deficiency. Admittedly there is no evidence of copper deficiency in disseminated sclerosis but an important role is played by this element in some enzyme systems.

Lead poisoning has been incriminated as symptoms and signs, similar to those in some chronic neurological conditions, have been observed in plumbism, and early workers reported raised levels of copper in the tissues of patients. Again recent work by better methods has contradicted these findings and it has been pointed out that in disseminated sclerosis other clinical stigmata of plumbism were absent. Here again lead may be completely involved in enzymic activity.

Hyperinsulinism has been shown to have a relationship to disseminated sclerosis in a very high percentage of cases and disseminated sclerosis is very rare in diabetics. Could glucose starvation affect the myelin?

Before leaving this field of speculation, one of the latest theories from Canada must be considered. Noble thought that disseminated sclerosis might be due to a deficiency of those fatty acids which are essential for myelin formation. He therefore fed a small group of patients with fatty acids of beef cerebrosides and claimed therapeutic improvement. When the

allergic theories are discussed it will be seen that this was perhaps a dangerous experiment.

The vascular and allergic theories are the most attractive and convincing of all.

Putnam noticed thrombi in some autopsy specimens and thought that these might be the cause of disseminated sclerosis particularly in view of the perivascular plaques. He conducted experiments in which he observed: (*a*) Demyelination akin to A.D.E. as a result of various thrombosing procedures in dogs; and (*b*) that in disseminated sclerosis the coaguability of the blood was increased. Other workers, however, though admitting the perivascular distribution of plaques and occasional thrombi, said that these were either secondary to vascular spasm, intimal damage, venous stasis and exudation which were seen histologically or due to a thromboplastic substance released from the plaques. The blood coaguability was lowered more often than it was raised in disseminated sclerosis.

Interesting evidence was put forward by Brickner who noticed vascular spasm in the fundal vessels with an associated scotoma. Vasodilator therapy cleared up these signs and he has even treated some patients with a continuous alcohol drip. This does not conflict with the findings of more permanent lesions since prolonged vascular spasm would obviously lead to changes which drugs could not affect.

Other workers have noticed general vascular changes such as spasm in the small vessels, and degrees of tortuosity and dilitation, which they believe are secondary to the spasm. While these changes were most noticeable in the lower extremity the effects of general vascular disease would surely occur first in the highly sensitive C.N.S.

Finally, in considering allergy in the C.N.S., some of the hypotheses tend to find a common denominator.

Clinically, the evidence for allergy is almost overwhelming: (1) the high incidence of other allergies, (2) the onset of these allergies just before the onset of disseminated sclerosis, (3) the course of the disease and the precipitation and aggravation of the disease by factors acting similarly on other allergies; nevertheless the poor response to A.C.T.H. and antihistamines and the somewhat more promising results of histamine-diphosphate therapy must be borne in mind.

Ferraro in 1946 compared the extent of the pathology with the manifestation of allergy, and abhorred the tendency of creating new disease entities out of minor histological differences. All these diseases, he said, could be understood and explained on an allergic basis.

Experimental parenteral injection of heterogenous or damaged homologous brain has produced demyelination in rabbits varying in intensity and character with the size and frequency of dosage and at the same time brain specific antisera were produced. The antigen was abundant in the white matter of the brain used, and it was never present in foetal brain in portions which had neither myelin nor oligodendroglia. How then can this be correlated with disseminated sclerosis?

By and large, attempts to incriminate known antigens have failed and the degree of correlation between disseminated sclerosis and other allergies of the C.N.S. is small. Perhaps, therefore, the secret lies in the property of damaged homologous brain tissue to act as an antigen and provoke a response within the brain. Anything which damages the myelin or oligodendroglia might set up a self-perpetuating auto-sensitisation. An antibody-antigen reaction would cause demyelination and provoke further release of antigen, in its turn increasing antibody production. The antibodies would of course

have to attain a critical level before a perceptible reaction could take place, thus explaining the relapsing and remitting course of the disease.

What conclusions can be drawn from this account? It is suggested that demyelination can follow a diversity of antecedents and is probably the least response of the C.N.S. to noxious agencies. The most satisfying explanation is auto-sensitisation to nervous tissue. "Disseminated sclerosis," said Kurland, "is not a specific disease but a syndrome with multiple aetiological agents and several mechanisms. An initial damage to the central nervous tissue with release of antigen finally perpetuates auto-sensitisation to nervous tissue."

INTERRUPTED FERTILITY *(continued from page 22)*

begins now to recover her appetite & gets strength, the bones always come away with a purging & some coagulated blood with, & after, her stools with a sharp tresmus.

During the summer she had passed several small bones, but her appetite & strength is much mended, having gone in a coach to Twitenham 4 miles distant from London, she was so ill from the jolting that she was obliged to be brought home in a chair and the day following seventeen bones mostly ribs were extracted, & as most of them lay transversely I was obliged to turn them & bring them away lengthways, this could not be effected without a great effusion of blood and the most excruciating pains. In October the remaining bones of the cranium came away all but one, these bones having three edges were always followed a profuse haemorrhage. In November she was troubled by the Whites & a heat in her urine. In December the largest and only remaining bone of the cranium was extracted, the swelling of her belly subsided, & she has recovered her strength greatly. In February 1776 her courses appeared & the next ensuing period, but both times by the anus, of which she made grievious complaint, I assured her they would soon come the natural way, which happened the May following, since the above she has been married to a second husband, by whom she had three childrine. The girl which she was delivered in October 1775 is still alive and a fine healthy girl.

HAZARDS OF RADIATION

Based upon a Dissertation given before the Society on Friday, 11th October 1957.

By ANDREW GUNN

Radiations are of two types: Particulate and Electromagnetic. Particulate radiations are comprised of the sub-atomic particles, electrons, protons, neutrons and alpha particles which, when moving at high speed, possess the property of passing through matter, the depth of penetration being proportional to their kinetic energy and their electrical charge.

Alpha Rays which are rapidly moving nuclei of Helium atoms have mass 4 and charge 2 on the atomic scale and have little power of penetration in tissue, reaching to a depth of about 0·05 mm.

Beta Rays which are beams of fast moving electrons, can penetrate tissue up to a depth of 2 to 5 mm., and

Protons with unit mass and electrical charge lie somewhere between these two.

Derived from an external source, these radiations are of little danger since they are obviously incapable of penetrating to the gonads and bone marrow, tissues in which the more sinister biological effects are manifest. These radiations are particularly dangerous when derived from a source which may be ingested with food and perhaps selectively concentrated in body tissues, as, for example, Strontium 90 in bone.

Electro-magnetic radiations comprise a continuous spectrum extending from long electrical waves of several thousand metres wavelength, through infra-red, visible and ultra-violet light down to soft and hard X-rays and gamma rays of wavelength 10^{-7} mm. and less. Radiations of very short wavelength, namely X and gamma rays, have the property of high penetration in tissues and along with them ultra-violet light may be considered as a penetrating radiation in fair-skinned people. Particulate radiations, together with ultra-violet light, X and gamma rays are collectively known as *ionising radiations* because they possess the property of ejecting electrons from the outer shells of atoms in their paths, these being taken up by neighbouring atoms with the creation of pairs of ions. Because of their ionising property these radiations can effect chemical changes in any solution through which they pass.

It is the degree and not the nature of the hazard that is new, for man has always been subject to irradiation from cosmic rays and radio-active materials in the earth's crust and atmosphere, together with radio-active elements within his body in small amounts, such as Radium in bone, Potassium 40 and Carbon 14. The dose from these sources is in the order of 0·1 rontgen (r) per year, a dose believed to be of slight significance on any reckoning. The dose received from natural background radiation in the first 30 years of life, accepted as the period up to the upper limit of average reproductive capacity, is thus 3r. The dose received from an ordinary chest film is only a fraction of 1r, but a gastro-intestinal examination with apparatus commonly in use may amount to 15r per minute. It has been calculated that the dose to the foetus during X-ray pelvimetry is of the order of 3r, a dose equal to that received from natural background in the first 30 years of life, and this even before the child is born.

Medical diagnostic radiology in which only a few sites such as the hip, lumber spine, abdomen and pelvis are important, undoubtedly forms the

most important source of man-made irradiation and its application is increasing steadily. While in Great Britain the genetic irradiation from this source has been estimated conservatively at 22 per cent.. of natural background radiation, figures for the U.S.A. and Sweden indicate that in these countries the dose from this source is equal to natural background.

Biological Effects

At the present time cellular damage from exposure to radiation is believed to be due to two causes:

1. Direct "hits" by the ionising particles or quanta striking and breaking the chromosomes—a purely mechanical process.
2. By the ionising of water contained in the cell very short lived oxidising radicals are produced which inactivate the cellular enzymes and may lead to cell death. This has been designated the "Poison Theory." Formation of these oxidising radicals is appreciably increased in the presence of molecular oxygen.

The proportion of cell damage to be ascribed to these two causes is unknown, but recent work suggests that the latter is just as important as the former, if not more so. It has been shown that the sensitivity of cells to irradiation is decreased if they are deprived of oxygen.

The desirability of protecting persons exposed to irradiation from military and civil sources has stimulated much research in radiobiology and this has been intensified since workers realised the importance of the "Poison Theory." It had formerly been thought that protection could be afforded only by shielding by physical means, but subsequently it was realised that chemicals might have a place to play in protection.

In considering methods of protection, the three important circumstances under which persons are likely to be exposed to irradiation must be distinguished:

1. Acute exposure to neutron and gamma radiation by persons in the vicinity of atomic explosions.
2. Exposure of patients to X-irradiation for therapeutic purposes.
3. Chronic exposure of persons in work carrying an occupational exposure, and to a lesser extent, of the general population who have been exposed to greater background radiation due to fall-out from nuclear tests and the increasing medical and industrial uses of X-rays.

Acute Exposure in War Time

Our knowledge is derived almost entirely from the reports following the explosion of atomic bombs over Hiroshima and Nagasaki in 1945. The majority of the 100,000 fatalities was due to blast injuries or severe burns, but in persons not so affected death was due to intense internal radiation following exposure to dense clouds of neutrons. The absorption of neutrons by the nuclei of certain elements, such as Sodium and Potassium, leads to the local emission by the now modified and unstable nuclei of more potent forms of radiation, and death results immediately from the intense chemical activity. In such circumstances protection is likely to be afforded only by screening by physical means. In persons farthest from the blast fatalities were due to severe radiation sickness like that often seen in a much milder form after radiotherapy. The severity of the illness varies according to the intensity of the exposure; when this was severe, death usually followed in a few days, but where the radiation was less intense the victims often survived several weeks. It is this last group that is most likely to benefit from chemical protective measures. The severity of the condition was much greater than that seen in civil practice; large numbers of the

irradiated victims developed widespread areas of necrosis in the mucous membrane of the alimentary tract which were responsible for the pernicious vomiting and intractable diarrhoea frequently preceding death. The exceptional vulnerability of the lymphatic and haemopoetic systems leads to extensive haemorrhages and renders the victim very susceptible to infection both endogenous, through the weakened resistance of the alimentary tract, and exgenous as a complication of wounds and burns.

Protective Measures

These fall into two categories:

1. Factors designed to render the tissues less susceptible to radiations.
2. Factors to counter the leucopenia and thrombocytopenia.

As has been pointed out the irradiation of water within the tissue cells produces highly active oxidising radicals and organic peroxides. These radiotoxins react with substances of physiological importance within the cells in the process already described as the "Poison Theory." The presence of oxygen alters the radiation chemistry of water, increasing the poisonous action, and also alters the state of the enzyme systems rendering them more susceptible to radiations.

Reducing agents may afford protection by reducing the oxygen tension. Sodium hydrosulphite, for instance, protects *B. coli* against six times the lethal dose of X-rays by producing anoxic conditions. Cysteine, cysteinamine and glutathione, when injected into animals all quickly lead to conditions favouring reducing reactions and when injected immediately before irradiation have protected animals from doses which would otherwise have been lethal. While the immediate poisonous effects may be considerably reduced by such sulphydral compounds, there is every indication that the genetic and carcinogenic hazards remain unaffected.

Other treatment consists of correcting electrolyte imbalance and administering antibiotics since in the early days after irradiation the body is virtually defenceless and death from bacterial infection is otherwise inevitable.

Dr J. F. Loutit, a Fellow of the Royal Medical Society, and his colleagues at Harwell have made interesting contributions to knowledge by showing that splenic and marrow suspensions could be used to protect against fatal leucopenia in mice by recolonising the bone marrow. They have cured leukaemia in mice by whole-body X-irradiation followed by injection of splenic and marrow suspensions. Though of great interest, this work has no practical significance for man unless the immunological problems can be solved. However, a lead shield to an appreciable area of the bone marrow would appear to be a small but practical protective measure in reducing the number of deaths from fatal leucopenia.

Radiation and Malignant Disease

The first cases of radiation induced cancer were reported only a few years after the discovery of X-rays and since then further cases have provided considerable material for study. As examples of these may be cited the skin tumours reported in the pioneer radiologists, the high incidence of leukaemia in survivors amongst the atomic bomb casualties at Hiroshima and Nagasaki, the high incidence of lung cancer in the Austrian miners at Schneeberg and Jáchymow, following inhalation of radioactive particles and gases, and the bone tumours found in workers in the luminising industry in New Jersey who, because of inadequate precautions, ingested minute amounts of paint rendered radioactive by Radium and Mesothorium. These are well estab-

lished facts but the radiation doses were all fairly high and whether these risks still hold when persons are continuously exposed to low dose rates will now be discussed.

Most, but not all irradiation-induced cancers occur in severely damaged regions; skin cancer is preceded by severe dermatitis and bone tumours by radiation osteitis. The tumours arise in the regenerating tissue which replaces the damaged, directly irradiated cells.

Tumours may be induced by three distinct mechanisms:

1. The induction of tumours in a localised normal region of the body by large doses of radiation may be described as the "Direct carcinogenic effect."
2. Radiations may act as carcinogenic agents and induce carcinogenesis in combination with other predisposing factors. Irradiation of tuberculous skin lesions may speed up the appearance of lupus cancers and irradiation of osteomyelitic lesions may result in osteogenic sarcoma.
3. An indirect or remote carcinogenic effect.

While the first two carcinogenic effects of radiation are local phenomena, the third is a systemic effect. In mice the incidence of ovarian tumours is significantly increased by small daily doses of gamma rays for over a year, or by a single large dose. If, however, one ovary is shielded from radiation and retains its normal function while the other is irradiated, the latter does not produce a tumour. If the experiment is varied and one ovary is excised while the other is irradiated, a tumour will be produced. Hormonal changes rather than a direct action of irradiation on the ovaries is implicated and this interpretation finds support in the observation that the grafting of an ovary from a speyed mouse into the spleen is followed by tumour formation in the grafted ovary. Under these conditions ovarian hormones are discharged directly into the portal circulation and are metabolised by the liver before they reach the systemic circulation. To compensate for the low level of ovarian hormones in the blood the pituitary increases its secretion of ovarian stimulating hormones which stimulate the ovary to hyperplasia and finally to neoplasia.

In medical practice the remote risk of inducing a new tumour by radiation therapy has to be accepted when this form a therapy constitutes the only hope of eliminating an existing tumour or at least of prolonging life.

Leukaemogenic Effects of X-rays

Animal experiments show that the incidence of leukaemia is increased by irradiation and this has been confirmed in man by evidence from the following sources:

Studies by the Atomic Bomb Casualty Commission show that the incidence of leukaemia amongst persons exposed to irradiation in Hiroshima and Nagasaki, and still resident there, is four times higher than that expected in a non-irradiated population, and further that the incidence is highest in those nearest to the site of the explosion.

In a recent survey under the auspices of the Medical Research Council, Court-Brown and Doll found that the incidence of leukaemia in persons irradiated for ankylosing spondylitis was ten times greater than in non-irradiated spondylitics, and there is obvious correlation between the dose received and the incidence of leukaemia. However, the total incidence of leukaemia in irradiated spondylitics is only one per thousand, so that it would appear justifiable to continue with this form of therapy which is the only one known to bring relief from pain and increased mobility to a large

percentage of sufferers. It is pointed out that the mortality for interval partial gastrectomy is 13 per thousand in the best hands.

Conditions of exposure to radiation in Japan and in the treatment of ankylosing spondylitis are not comparable with radiation in small doses over long periods which might be received by persons engaged in work carrying a radiation hazard. There is some evidence to show that there is an increased death rate from leukaemia in radiologists, but knowledge of the occurrence of leukaemia under conditions of chronic exposure is too scanty to allow any reliable conclusions to be drawn. Most workers have found the life expectancy for radiologists to be no shorter than that for other medical specialists.

The potentially leukaemogenic nature of X-rays is emphasised by Dr Alice Stewart and her colleagues, whose findings suggest that exposure of children to X-rays during pre-natal life may be an aetiological factor in the development of leukaemia in infancy and childhood. It is probable that the foetus is more susceptible to the leukaemogenic effects of radiations than either children or adults.

In the belief that the incidence of chronic lymphatic leukaemia is not increased by exposure to X-rays (and this was also a finding amongst the atomic bomb casualties) workers studied the differences in the frequency of a history of exposure to X-rays for therapeutic or diagnostic purposes amongst patients with this form of leukaemia and amongst those suffering from acute leukaemia and chronic myeloid leukaemia. It was found that a history of exposure to X-rays was given in significantly greater frequency by patients with acute leukaemia and chronic leukaemia than by those with chronic lymphatic leukaemia. These studies suggest for the first time that the comparatively low dosages of X-rays received in diagnostic procedures may induce leukaemia.

The nature of the relationship between the incidence of leukaemia and the dose of X-rays, and consequently an understanding of the scale of risks involved, remains to be discovered. It is of great importance to determine with some degree of confidence whether a threshold exists below which exposure is not associated with an increased incidence of leukaemia. Many consider that the possibility of very small doses of X-rays being able to induce leukaemia cannot be ruled out. Research is needed to diminish the risks still further but not at the expense of effective treatment and accurate diagnosis.

Strontium 90

There is also much concern on account of the potential somatic dangers from internal radiation from the radioactive isotope, Strontium 90. This is a particularly dangerous fall-out product from nuclear tests because:

1. It has a high yield.
2. It is chemically similar to Calcium and finds its way into the Soil—Plant—Animal cycle of Calcium.
3. It is largely retained in the skeleton.
4. It has a long biological half-life (7½ years).

It has been known for many years that ingestion of Radium and Thorium by the workers in the luminising industry is followed in a large proportion of cases by bone lesions including osteogenic sarcoma. Like Radium, Strontium is selectively concentrated in bone and the beta rays emitted may produce bone tumours, or leukaemia by marrow irradiation. The hazard has long been recognised but too little is known to assess it quantitatively. American work indicates that the doses which produce

sarcomatous change are extremely small. The fundamentally important question is: "How does tumour formation vary with dose?" If a threshold exists below which tumours do not develop then the small doses resulting from test explosions are probably harmless. If, however, there is no threshold and tumour formation is a linear function of dose, even the smallest dose will impart a small but definite probability of a bone tumour being formed.

It is the genetic effects, however, that have caused the greatest concern. The hazard to the human species from the genetic point of view arises from the fact that radiations have the property of inducing mutations. Some workers have suggested that the production of mutations in somatic cells accounts for carcinogenic and leukaemogenic effects of radiations. As far as is known, radiation induced mutations are in every way comparable to natural mutations, but it is unlikely that natural background radiation contributes more than between 2 and 22 per cent. of spontaneous mutations.

One of the most outstanding features of a mutation is its complete irreversibility. There can be no question of repairing the damage done since each gene is the jig upon which its progeny is constructed. Genetic mutation is thus cumulative, and long continued exposure to radiation of low intensity induces as much gene mutation as an equal dose of radiation of higher intensity. There is no going back in heredity; damage once done cannot be undone. As Muller has pointed out we are but the trustees of our own germplasm; it is the property of our offspring, and, indeed, of the whole human race.

In considering radiation hazards particular interest has been focused on the low range of doses and on the delivery of radiations at very low intensity. Before one can assess the hazards quantitatively one must know whether there exists a threshold below which radiations do not have deleterious effects. I have tried to show that when considering genetic damage the idea of a threshold does not apply since mutations, once induced, are irreversible, and since the minimum amount of incident radiation is capable of inducing genetic mutation.

The theory that radiation induced cancer, or indeed all cancer, is due to somatic mutation, brings into the same focus the two most important harmful effects or radiation, namely carcinogenesis and genetic damage. If this theory is correct, very serious consequences may be expected from nuclear tests already carried out.

Using *Drosophila*, workers have shown that there is no departure from a linear relationship in experiments with acute doses down to 25r. Moreover, the regression line through their experimental points cuts the axis at zero dose at a value not inconsistent with the observed rate of mutation in non-irradiated controls. Even if this work is substantiated it would not be justifiable to assume that the same conditions hold for man; but it should serve as a solemn warning to all that great hazards may attend the use of X-rays and even the relatively small contributions made to natural background radiation by fall-out from nuclear tests. It is probable that there is no dose below which radiations are harmless, and even with very small dose rates ill effects will be seen if a sufficient number of people are observed. The genetic effects of atomic radiation would be wholly bad because they would increase slightly the sum of misery and wastage against which the race has to battle, but, longterm though some of the consequences are, they are unlikely to hamper the course of human progress in the widest sense of that expression.

All references quoted in the Dissertations may be consulted in the original papers on the Society's premises.

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