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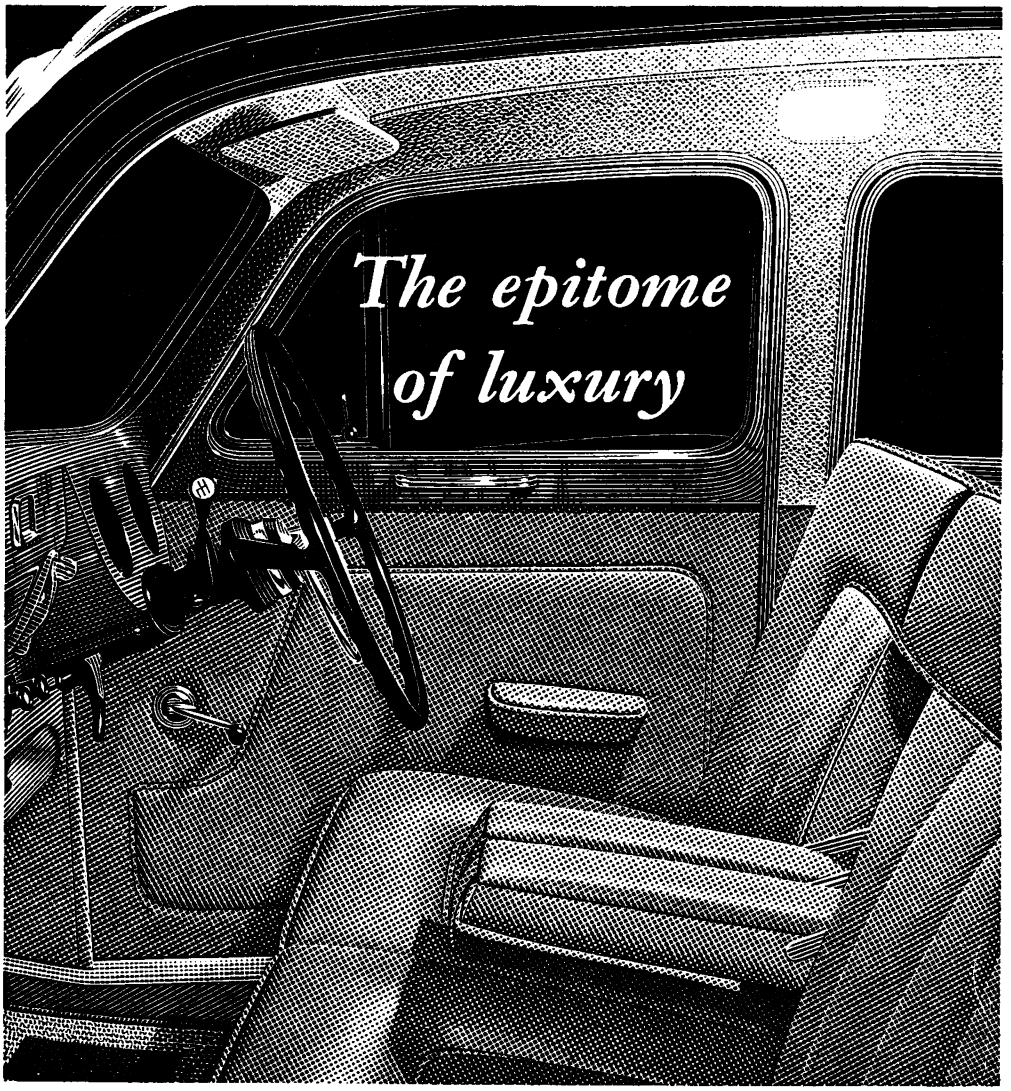

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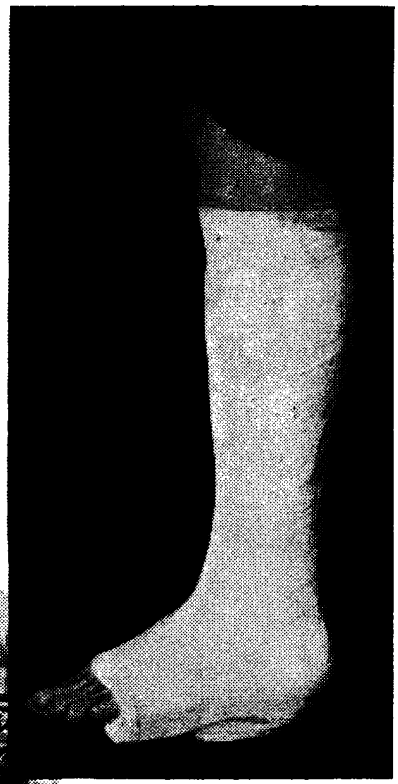

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THE
ULSTER MEDICAL JOURNAL

PUBLISHED ON BEHALF OF THE ULSTER MEDICAL SOCIETY

Vol. XXVIII 1st MAY, 1959 No. 1

PSYCHOPHYSICAL RELATIONSHIPS

By **JOHN G. GIBSON, M.D., M.R.C.P.(Lond.), D.P.M.**
Professor of Mental Health, The Queen's University, Belfast

ABRIDGED FROM AN INAUGURAL LECTURE
delivered at The Queen's University of Belfast, Wednesday, 4th February, 1959

THE approach to the subject of this lecture is dictated by two of the most important principles held by the Medical Faculty of this University in the teaching of medicine.

The first of these is that the student should acquire a sound knowledge of the laws governing health and disease, so that no matter what problem confronts him as a doctor, he will be able to marshal his facts in such a way that even if they are not sufficient to make a complete diagnosis, he will be able to put forward a sound working hypothesis.

The second principle is equally important—and is perhaps more a reflection of present-day trends in medical thought than is the first. It is that the teacher should be prepared to lose his identity in so far as the boundaries of his department or speciality are concerned, and follow his subject where it is relevant to other specialities. In this way, better than in any other, the student will realise that departments are created mainly for administrative convenience, and not because they represent isolated bodies of knowledge.

Psychiatry urgently needs objective criteria whereby the phenomena observed can be measured, and whereby those measurements can be repeated by other observers. Only thus can we establish sound principles that may well be the key to some of the most stubborn problems of medicine.

The study of psychophysical relationships is of great importance in the present state of our knowledge. It would be contrary to the facts to claim that it is the only approach, but it is one to which the scientific method can be applied with the greatest chances of success.

The late Professor Walmsley used to emphasise that growth and development did not take place at a uniform rate. Phases of comparatively rapid growth were followed by phases of relative quiescence. The same is true of the history of medicine and psychiatry. The nineteenth century saw men like Virchow making great contributions to clinical medicine and pathology, and Claude Bernard establishing the discipline of experimental physiology, which was to become such an essential part of medicine. Their efforts resulted in attention becoming increasingly turned to the soma, to such an extent that mention of the psyche would almost imperil the professional reputation of anyone who dared to do so. In the conquest of physical disease their approach yielded great dividends, but it was not enough. The patients themselves kept alive that part of the art of medicine that had to do with human relationships. Doctors had to continue to deal with people who were ill, and not with diseases taken out of their human context.

Zilboorg (1941), a modern exponent of the human approach from the psychoanalytic standpoint, has pointed out that in psychiatry the discovery of the cause of G.P.I., in addition to its being a momentous step forward in the history of medicine, had rather unfortunate side effects. He claimed that attention was turned away from psychogenesis, and physical causes for mental illness were sought with renewed vigour. Voices were silenced, that had in the past claimed that not all diseases of the brain produce psychological symptoms, and that not all psychological symptoms are due to demonstrable pathology. The readiness with which this occurred has an historical basis which is just as important today as it was then. There exists still a deep-rooted fear of the supernatural, and many people regard mental illness either as a form of Divine punishment or demoniacal possession, thus placing it outside the legitimate province of medicine. Many doctors share society's attitudes towards psychiatry, and those of their number who propound theories of psychological causation are sometimes rather severely criticised, and regarded as having strayed from the fold of medicine. Should a physical cause for a mental illness be discovered, these attitudes are further crystallised. Similarly, should any theory strike at the foundations of the generally accepted picture of man at the time, its author suffers at the hands of medical and other orthodoxy. Freud suffered this fate: he advanced too far, too quickly, into the prohibited territory of what was considered to be supernatural. He encountered the same attitude on the part of the medical profession, few of whom know of his work as a neurologist, not because he was not a sound one, but rather because it is difficult to recognise him as such because of his deviationist beliefs.

Almost four centuries earlier Johann Weyer, one of the first physicians to take a major interest in mental illness, embarked upon a detailed systematic examination of the phenomena of witchcraft. His analysis of the evidence left no doubt but that he regarded it as a manifestation of mental illness and not the result of evil spirits. The force of his logic failed to impress either priest or physician, and his writings were ignored for a long time after his death.

These examples serve to illustrate two trends of thought concerning psychiatry; on the one hand that given great impetus by the work of Virchow that psychiatry is solely and firmly on the path that leads to the fold of purely somatic medicine;

on the other hand that begun by Weyer and epitomised by Freud in our time that what was formerly attributed to the supernatural was, in fact, natural and capable of a psychological explanation. It was the disciples rather than the author of psychoanalysis who burned their boats, for Freud believed that his system of psychology would ultimately be replaced when the basic scientist bridged the gap between the psychological phenomena and their somatic counterparts.

We have much tangible evidence today that the attitude to psychiatry is being tempered more by reason and less by prejudice. The revolution that is taking place in England is being given practical expression in the proposed changes in the law relating to mental illness. Medicine too has broadened its basis in that the study of the social impact of disease has become one of its disciplines. Pavlov and Cannon were pioneers in widening the scope of experimental physiology. The effects of emotional stress can now be observed in the laboratory, and assessed with a degree of scientific accuracy that is acceptable to any physiologist. In the laboratory, too, psychology and behavioural physiology become virtually indistinguishable. Thus we have the scientific basis of medicine including as a subject for legitimate study the importance of the emotions in bodily changes, whilst those in the basic sciences work more and more on the problems of psychiatry. It is no longer essential for the union of psychiatry and medicine that the former should become entirely mechanistic. Each is drawn to the other by a common interest. Neither can be scientific without the other, for it is unscientific to ignore facts no matter where they lead. Boundaries are being broken down and the old dichotomy of mind and body is as untenable as it is out of date.

The argument in favour of this fusion is put forward very strongly by Cobb (1958). He claims that unless supernatural phenomena are accepted there can be no question of functions of man other than "organic" ones. For him there is no such thing as "the inter-relationship of mind and body," for organic change must take place whenever a person thinks. He holds that it is illogical to regard the knee-jerk as a physical reaction, whilst at the same time calling the more complex phenomena of the nervous system, such as memory, 'mental,' unless one accepts that the dividing line between the two is entirely arbitrary, its position depending upon the point to which technology has advanced. Penfield and Milner (1958) have recorded that removal of a particular part of the brain, namely, one hippocampal zone, in the presence of a destructive process in the other, produces very serious recent memory loss. This finding strongly supports Cobb's contention.

Many of our difficulties could be overcome if it were more generally recognised that in our several disciplines the object of our study is the same, although we use different techniques according to the particular aspect of the individual in which we are interested. Nobody will question the fact that a disease such as G.P.I. has both a pathology and a psychopathology. The pathologist can describe the physical basis for the disease, but he cannot explain the content of any delusional beliefs held by the patient. These are understandable only when one takes into account the personality of the patient before the illness began. It had been hoped that different physical illnesses, when accompanied by psychological

disturbances of a major kind, would produce characteristic mental states. These hopes have not been fulfilled. The kind of person who becomes mentally ill as the result of structural disease is far more important in determining the form and content of the psychiatric disturbance than is the structural disease itself. By using both the physical and the psychological approach together it is often possible to arrive at a much better understanding of an illness than would otherwise be the case. In treatment, too, the psychotherapeutic approach can often have a very beneficial physiological effect in certain psychosomatic illnesses, just as it is possible for the physical approach in certain instances to break a psychological vicious circle.

The anatomical pathways through which the activity of the body can be influenced by emotional states have not been neglected. The visceral brain or rhinencephalon and its connections include such parts as the olfactory, visceral, hippocampal, hypothalamic, and pituitary structures. All these are closely integrated so that sensation and bodily reactions are co-ordinated. For instance, smell, which once played such an important part in primitive search and feeding, has sensory pathways which eventually convey impulses to the hypothalamus, and also ultimately has connections on the motor side. Even today it has not lost its importance as evidenced by the cosmetics industry and the number of words in the language directly related to it. The hippocampal gyrus receives some information concerning sensation of all kinds from all the surrounding areas of the brain. It has been suggested that some degree of integration and modification of information takes place here, the result being various moods. Papez (1958) claims that atrophic changes can be found in the hippocampal gyrus in patients in whom mood disturbances were prominent during their lifetime.

The hypothalamus which has important afferent and efferent connections with the prefrontal areas, thus bringing it within the orbit of the so-called "higher centres of the brain," interests equally the physician, the physiologist, and the psychiatrist. This area can be regarded as the head ganglion of the automonic nervous system. Its primary concern is the integration and exteriorisation of emotion. It is not the site where emotions are experienced by the individual. This group of nuclei is concerned with bodily needs: temperature, respiration, blood pressure, water balance, electrolytes, carbohydrate metabolism, and the functions of the pituitary body are all involved. It is here that the necessary adjustments in bodily economy are made to meet the demands of everyday life in all its aspects. Walter Cannon was one of the pioneers who did so much to enable psychiatrists and physiologists to understand one another. He showed that oxygen lack, low blood sugar, hæmorrhage, cold and fever all resulted in a sympathetico-adrenal discharge that was necessary to restore the organism to normal. The hypothalamus plays a very important part in this functional restoration.

It is now known that hypothalamic activity is much more far-reaching in its effects because of the relationship of that structure with the pituitary body. It is easy to understand how nervous activity can influence the secretions of the posterior pituitary because of the direct nervous link between it and the

hypothalamus. The anterior pituitary or adenohypophysis, on the other hand, has no nervous connections with the brain, but Popa and Fielding and Wislocki described a vascular network which is the anatomical basis for hypothalamic control of the anterior pituitary. Green and Harris (1949) established by direct observation that the direction of blood flow in these vessels is from the hypothalamus to the pituitary. It is through these portal vessels that substances travel from the hypothalamus to the anterior pituitary, and control the secretion of hormones that govern gonadal, thyroid, and adrenal cortical activity. It is also known that a reciprocal relationship exists in that these hormones react in turn on the nervous system, and that they exert a feed-back effect on the anterior pituitary.

As an example of the processes involved, I would like to give you an account of some work designed to explore the factors modifying thyroid activity and how they operate. Physicians, surgeons, and psychiatrists are all interested in factors modifying thyroid activity. The first reference in the literature to thyroid over-activity drew attention to the fact that emotional factors might be important. Ten years before it was called Grave's Disease; Parry, in 1825, described the development of hyperthyroidism following a severe fright. There has been a wealth of references to the importance of emotional factors in this condition ever since. Before the advent of modern pre-operative preparation, surgeons were keenly aware of the dangers of injudicious management of their patients. They realised that if the patient were not suitably prepared psychologically for the operation, their technical skill might be of little avail.

The general physician and the psychiatrist share a common interest in under-activity of the thyroid gland. Its early recognition in an infant may make all the difference between normality and a life-time of intellectual dullness. In an adult, replacement therapy may reverse the picture of dementia or prevent the occurrence of associated psychoses. Thus the patient has everything to gain from this fusion of disciplines.

There are wider issues at stake. It is comparatively easy to study the activity of the thyroid gland in the living subject, both because of its superficial position and because of the readiness with which modern radioactive techniques can be applied to this study. Apart from thyroid dysfunction, the thyroid gland can be used as an indicator of the effects of emotional stress on one aspect of anterior pituitary activity.

The work that I will describe was carried out in the Department of Neuro-endocrinology, of the Institute of Psychiatry, Maudsley Hospital, London, by Professor G. W. Harris, and those of us who had the privilege to work with him or under his guidance.

In order to study the functional relationship between the central nervous system, the anterior pituitary gland, and the thyroid, a technique had to be developed whereby measurements of thyroid activity could be carried out repeatedly over a period of several weeks in the conscious animal. The use of tracer doses of radio-active iodine made this comparatively easy, and much more accurate than any method previously employed. Professor Harris, together with

Doctors Brown-Grant, von Euler, and Reichlin (1954), adapted a method for rabbits whereby they could be maintained comfortably in the conscious state in a constant geometrical relationship to a suitably screened geiger-Muller tube. Only radio-activity in the thyroid gland and its immediate surroundings was measured. They found that after a three-microcurie dose of radio-active iodine given intravenously, the maximum accumulation of ^{131}I in the thyroid occurred between 12 and 48 hours. After this time the radio-active content of the thyroid gland decreased exponentially with time. Suitably plotted, this gives a straight line, after correction for decay. The falling off in the counting rate over the thyroid gland is due to the release of radio-actively labelled hormone. This technique then provides a direct measure of thyroid activity. Changes in the slope of the curve are immediately related to changes in the rate of release of hormone. It can be shown that thyroid stimulating hormone or TSH produces a marked increase in the rate of release of protein-bound radio-iodine within one to three hours after a single injection. Thyroxine, on the other hand, will produce a complete inhibition of release, as indeed will hypophysectomy.

The emotional stress induced by physical restraint, if it is varied during the experiment, will cause an inhibition in the rate of release, in some cases for 24 to 48 hours, in others for as long as the restraint is applied. Afterwards the animal will resume approximately its original rate of release of radio-active labelled hormone. Large doses of adrenaline will also inhibit the thyroid activity. Now, if the animal's adrenals are removed and it is maintained on cortisone, emotional stress will still inhibit thyroid activity, but it will do this less constantly than it would in the intact animal. If normal animals are given either A.C.T.H. or cortisone, thyroid activity will be inhibited. This suggests that there is a reciprocal relationship between the activity of the thyroid and the adrenal cortex.

It is rather difficult to reconcile this finding with what occurs in the human subject especially if it be true that emotional stress which stimulates the adrenal cortex plays an important part in the causation of Grave's Disease. Harris and Woods (1956) have investigated this problem. By combining a technique for electrical stimulation of the median eminence of the hypothalamus and the release curve technique that I have already mentioned, they found that they could inhibit thyroid activity in most of their experiments. This was not surprising, for it is known that such stimulation will activate the adrenal cortex via the pituitary, and that this in turn will inhibit the secretion of thyroid stimulating hormone. However, when they removed the animals' adrenals and gave them a steady replacement dose of cortisone, hypothalamic stimulation resulted in anything up to four-fold increase in thyroid activity. They suggested on the basis of these findings that there may be a relative, if not an absolute reduction in adrenal cortical activity in thyrotoxicosis. If the latter were proven, it would provide an explanation why emotional stress should result in markedly increased thyroid activity in the human subject. They cited some supporting evidence that claimed that adrenal cortical activity in thyrotoxic patients was low normal or reduced.

Dr. Willcox, the Clinical Pathologist at the Maudsley Hospital, and myself looked for evidence of thyroid adrenal reciprocity in patients in whom there was

no reason to believe that either thyroid or adrenal cortical activity was abnormal (Gibson and Willcox, 1957). We made repeated measurements both of thyroid and of adrenal cortical activity in these patients from daily to weekly intervals for periods up to three months. Our findings did not demonstrate any constant relationship between the activity of the thyroid and the adrenal cortex. In one patient we observed the effects of thyroxine withdrawal when marked changes were taking place both in the activity of the thyroid and of the adrenal cortex. We were unable to demonstrate any clear inverse relationship between the function of these two glands. In one patient in whom thyroid function was still abnormal after surgery, we did not observe any clear-cut reciprocal changes. Next, we measured adrenal cortical activity in six cases of proved thyrotoxicosis. In five of these the 24-hour urinary 17-ketosteroid excretions were high normal or increased. It would appear then that fluctuations in adrenal cortical activity occurring within physiological limits, and measured by the techniques mentioned, are not accompanied by large inverse changes in thyroid activity in the group of patients studied. Similarly, absolute adrenal cortical hypofunction is by no means a constant finding in thyrotoxicosis. The possibility of relative adrenal hypofunction, however, could not be excluded.

The findings in the experimental animal that under certain circumstances hypothalamic stimulation results in increased thyroid activity raises two important questions in an illness that has long been regarded as in some way related to the effects of emotional stress. It throws doubts on the validity of the often-repeated statement that thyrotoxicosis can follow immediately an acute emotional trauma in an individual whose adrenals are presumably healthy. Secondly, it raises the question as to whether or not long continued stress might be the operative emotional factor in the condition.

Many doctors are becoming less certain that acute emotional stress often immediately precedes the onset of the disease. Reports that battle stress may be a precipitating factor do occur, but there is a very interesting observation that no cases of thyrotoxicosis could be found after any naval action in the First World War (1933). There is, perhaps, too ready a tendency to select isolated incidents and to invest them with an importance that they do not possess.

The second hypothesis, namely, that long continued emotional stress might be the operative emotional factor, finds some support in the literature. It has been repeatedly stated that the personality of the patient before the illness began possesses certain characteristics which are distinctive, and which remain even after surgical treatment. A very interesting study of eighty-four patients carried out in America (1956) showed that although in seventy-one of these there was evidence of some stress preceding the onset of thyrotoxicosis, it was within the realm of usual life experiences and of a kind liable to be experienced by everyone —for example, bereavement. The conflict situations uncovered by a comprehensive battery of psychological tests and interviews were as varied as those seen in neurotic and psychotic patients generally.

If we combine all the evidence put forward so far we can say that in a predisposed individual in whom certain personality characteristics are present

there is a tendency to react specifically to the commonplace stresses and strains of life over a period of time; that ultimately the adrenal cortex is no longer able to respond as before, and thus the thyroid is given free reign. Whether this speculation is sound or not can only be determined by the physiologist, biochemist, endocrinologist, and psychiatrist working together. What is certain is that no single discipline working in isolation will provide all the answers to this complex problem.

It is unfortunate that we cannot readily study the rate of release of thyroid hormone in the human subject as can be done in animals. This is because the hormone is released into the blood stream so slowly, and in such small quantities, in normal subjects, that we cannot readily measure any change. It is much more feasible to measure the rate at which the thyroid gland takes up iodine in order to convert it into thyroid hormone. It is important to know whether or not this uptake is under the control of the central nervous system, and whether or not a short-lived stress can effect it in other ways, for instance whether the adrenaline released has any effect. Clinicians know that such stress can have a very serious effect on an uncontrolled thyrotoxic patient, and that drugs antagonistic to adrenaline can greatly benefit such patients.

Dr. Brown-Grant and I explored the problems of thyroidal uptake of radioactive iodine experimentally (1955). We had to ensure that the rabbits were comfortably positioned as most of the experiments we wanted to do were in the conscious animal. It was possible to aim the scintillation counter at the rabbit's thyroid and to reproduce this position when necessary. Having determined that there was minimal background radio-activity, and that it remained constant throughout the experimental period, we then had to show that the rate of uptake actually measured thyroid activity. In other words, that the iodine that was taken up by the thyroid gland was actually used in the manufacture of thyroid hormone. That this was so was shown by the fact that it was only when the animals were pretreated with thiouracil that potassium thiocyanate produced a rapid and complete discharge of radio-activity from the gland. In other words, it was only when a substance was given that would prevent the formation of thyroid hormone that the iodine in the gland could be discharged by another drug.

Having established the validity of the method, we then proceeded to investigate the possible effects of adrenaline on the rate of uptake of radio-iodine, and attempted to assess its physiological significance. From the psychiatric standpoint it was important to know what effects short-lived stresses had on thyroid activity, whether they came under the jurisdiction of the hypothalamus via the pituitary, or whether adrenaline had a local effect on the thyroid. Uptake experiments might provide us with more information on these points (1956).

It was not until we gave a long-acting preparation of adrenaline that we observed a marked or complete inhibition of uptake. Continuous intravenous infusion of adrenaline bitartrate at the rate of 2 microgrammes per minute resulted in a complete cessation of uptake. After stopping the infusion the uptake continued more rapidly than before. A striking difference was noticed between the dosage of adrenaline necessary to produce this effect and that of nor-

adrenaline. It required sixteen times the amount of adrenaline for nor-adrenaline to produce any effect.

We knew that our dosage of adrenaline was equivalent to what a rabbit could produce from its own adrenals. That the phenomenon was a physiological one was supported by our finding that large doses of insulin, a substance known to produce selective release of adrenaline, resulted in an inhibition of uptake. This effect was abolished by giving the animal glucose.

Another stimulus to the release of adrenaline, namely, laparotomy under anæsthesia, resulted in a marked reduction or complete cessation of uptake. We were able to show that these effects were due to the animal's own adrenaline rather than to the local sympathetic nervous supply to the thyroid gland for neither insulin nor laparotomy effected the rate of uptake in the series of animals in which the adrenals had been removed. Again it was unlikely that the effects observed were the result of anterior pituitary activity for when we gave a series of animals thyroid stimulating hormone during an uptake measurement, no effect was observed on its rate.

From these results it would seem that the initial response of the thyroid gland to emotional stress is under the control of the adrenal medulla, and that this response merges with the phase where a presumed decrease in pituitary thyroid stimulating hormone secretion causes a reduction in the rate of release of the thyroid hormone.

In so far as experimental findings in animals can be applied to man, it would seem that these results give us some reason to look again at our clinical observations. There is no experimental evidence so far to suggest that a sudden short-lived stress will result in over-activity of the thyroid gland in a normal person. There is some evidence, however, both in animals and in man, that where the adrenal cortex is unable to respond normally to stress, an increase in thyroid activity does occur. Long-continued or often-repeated emotional stresses therefore would seem to be more likely to result in thyrotoxicosis in a pre-disposed person than would a sudden short-acting stress. The results of the uptake experiments support this view. The release of adrenaline by a short-lived stress does not seem to play a vital rôle in the hormonal activity of the gland. We do know, however, that thyroid hormone potentiates the action of adrenaline, and to this extent the intense vascular response that can be seen readily in the exposed thyroid is a temporary protective mechanism.

At the beginning of this lecture I said that principles were important. If medicine and psychiatry are truly to become one then there is no more important principle than that which maintains that emotional stress can have a profound effect on the bodily function, and vice versa. I have tried to present you with the experimental evidence that I believe strongly supports this view in the case of an endocrine gland which has such widespread effects on bodily metabolism. It is also logical to conclude that where stresses can be relieved by psychological treatment that such treatment will favourably influence bodily activity. In any physical condition where it has been shown that emotional factors play a part

either in the causation or precipitation of the illness, then psychotherapy should play its part in the treatment of that condition.

Many laboratories at the present time are vigorously engaged in the pursuit of information concerning the physiological and biochemical concomitants of mental illness. Where we can measure changes and reproduce those measurements, we will have laid the foundation stones for rapid advance in the conquest of psychiatric illness. By a close study of every aspect of psychophysical relationships we may well discover the key to two kinds of illness that form the bulk of the psychiatrist's practice, namely, depression and schizophrenia. However, no matter what advances are made, there will always remain in every aspect of medicine a vital need for the understanding and skilled management of human relationships.

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HÆMOPHILIA IN NORTHERN IRELAND

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AMONG the bleeding disorders, hæmophilia has always attracted the greatest interest. The familial nature of the disease, its early onset in life, its predilection for males, and the inefficiency of the blood clotting have all been recognized. Recent work, however, has cast doubt on the long-established view that hæmophilia is a single entity. It has been shown that all cases, which present clinically as hæmophilia and which have a characteristic hereditary pattern, do not necessarily have the same basic defect in the blood. Indeed the impaired blood coagulation may be due to the deficiency of one of three clotting factors. As it is impossible to differentiate these types of hæmophilia on clinical grounds the final diagnosis can only be made in the laboratory.

In 1955, in co-operation with the Medical Research Council, we carried out a survey of all possible hæmophilics in Northern Ireland. We began with a nucleus of patients already known to us. With the help of the Northern Ireland Hospitals Authority and Northern Ireland General Health Services Board, we were able to approach the great majority of family doctors and consultants in Northern Ireland, from whom we received every co-operation. Although no survey of this kind can claim to be complete, we believe it to represent the majority of the "bleeders" in Northern Ireland. We established a register of all hæmophilics in this area and offered facilities for the treatment of bleeding episodes. In co-operation with the Dental Department of the Royal Victoria Hospital, we introduced a service for regular dental inspection and conservative treatment.

We feel that the information obtained during this survey and our subsequent experience in management are of sufficient general interest to warrant publication.

WHAT IS HÆMOPHILIA?

The older workers recognized this disorder by the presence of a classical triad which consisted of:—

(*a*) A persistent bleeding tendency in a male appearing in early life.

(*b*) A positive family history or characteristic hereditary pattern.

(*c*) A delayed blood-clotting.

While not all cases show the combination of typical clinical manifestations, characteristic hereditary pattern, or evidence of delayed blood-clotting, yet all have a deficiency in a blood-clotting factor. Nowadays the more modern laboratory tests have allowed the precise determination of the clotting factor responsible for this bleeding disorder. This has led to the discovery that cases of hæmophilia with similar clinical and hereditary manifestations may have

different clotting factor deficiencies. The factor which is deficient in classical hæmophilia is antihæmophilic factor. Biggs, *et al.* (1952), described some cases of a hæmophilic-like condition which was due, not to a deficiency in anti-hæmophilic factor, but to another factor also necessary for thromboplastin formation. This was called Christmas factor after the surname of the first patient in whom the defect was recognized. This factor is probably identical with plasma thromboplastin component deficiency described independently by Aggeler, *et al.* (1952), in America. More recently Rosenthal, *et al.* (1953), have described a hæmophilic-like disease with deficiency of a factor, which they call plasma thromboplastin antecedent. Thus at least three types of hæmophilia exist. These are often referred to as classical hæmophilia or hæmophilia A, Christmas disease or hæmophilia B and plasma thromboplastin antecedent deficiency or hæmophilia C.

We have discovered, just as in other surveys of this kind, that there are clinically mild cases of classical hæmophilia who show a definite deficiency in antihæmophilic factor. Such patients may only bleed when subjected to gross trauma or operative procedures. The possibility of a bleeding disorder may not be seriously considered on clinical grounds and is only brought to light by laboratory tests. Hence classical hæmophilia cannot be entirely restricted to the clinical syndrome but must depend mainly for diagnosis on the laboratory findings. We have, therefore, utilised the following criteriæ for the diagnosis of classical hæmophilia: (*a*) a history of a bleeding tendency; (*b*) a qualitative deficiency of antihæmophilic factor; (*c*) a quantitative level of less than 30 per cent. of antihæmophilic factor. The hereditary pattern was also investigated and is discussed later. As a characteristic pattern was found in less than half the cases investigated it was only used as corroborative evidence.

Laboratory Tests used in Diagnosis.

During the course of this investigation five tests have been utilised for the diagnosis of hæmophilia.

1. *Clotting Time.*

The capillary technique for the determination of the clotting time is capricious and therefore generally regarded as unsatisfactory. The tube technique of Lee and White (1913), which attempts to ensure that an equal area of water-wettable glass surface is exposed to the blood, provides more reliable and reproducible results. By this method normal blood should clot within ten minutes.

2. *Prothrombin Time.*

This test is normal in hæmophilics since the added tissue thromboplastin is able to convert prothrombin to thrombin in the presence of calcium and hence change the fibrinogen to fibrin.

The prothrombin test will detect deficiencies in prothrombin, factor V and factor VII, and thus separate these disorders from the hæmophilic states. It is, therefore, a useful screening test.

3. *Prothrombin Consumption Test.*

When normal blood coagulates, the prothrombin is utilised in the process and consequently very little can be detected in the serum an hour after clotting is complete. The results can be expressed either as the percentage prothrombin consumed or as the prothrombin activity of the serum. This latter test is called the serum prothrombin activity (S.P.A.). The presence of less than 20 per cent. prothrombin in the serum an hour after clotting can be regarded as normal.

It has been shown that the serum may still contain considerable amounts of prothrombin an hour after blood from a hæmophilic has clotted. This test is, therefore, a somewhat indirect way of determining the efficiency of thromboplastin generation. It is not specific for hæmophilic states as it may also be defective in conditions associated with thrombocytopenia.

4. *Thromboplastin Generation Test.*

It was the introduction of this test by Biggs and Douglas (1953) which made possible the accurate diagnosis of hæmophilia and its clear separation from other coagulation defects. The development of the thromboplastin generation test has been largely responsible for a world-wide impetus to the study of hæmophilia.

The principle of the test is to measure in vitro the rate at which thromboplastin is generated by the blood of an individual. Any significant reduction in the amount of any of the coagulation factors will reduce the rate of thromboplastin generation. In our hands we have found the thromboplastin generation test a satisfactory way of diagnosing hæmophilia. Usually a diagnosis of hæmophilia can be made without the use of blood from a known hæmophilic patient. However, in some mild cases we have had to use hæmophilic plasma in order to determine whether the plasma of the patient will correct the defect of a known hæmophilic patient.

5. *The Antihæmophilic Factor Assay.*

The assay of the amount of antihæmophilic factor present in the plasma is of considerable value both in the diagnosis and in the management of hæmophilia. We have found the method of Pitney (1956) to be most satisfactory from the technical point of view and to give reproducible results.

The Incidence of Hæmophilia in Northern Ireland.

It is generally agreed that the incidence of hæmophilia is probably greater than most people believe. Since more extensive surveys have been carried out, the actual incidence has been found to be much greater than the hitherto accepted or known incidence in the area involved. In Northern Ireland the total number of "hæmophilics" so far discovered has been forty-three in a total and fairly stable population of 1.75×10^6. Of these, thirty-nine were cases of classical hæmophilia giving an incidence of 1 in 45,000 for this disease. This is comparable with the incidence given by Biggs and Macfarlane (1954) of two or three hæmophilics per 100,000 inhabitants in England.

In any consideration of the epidemiology of hæmophilia there should be some reference to the incidence of the different genetic defects. Among our cases we have found no examples of plasma thromboplastin antecedent deficiency or hæmophilia C. Like other workers, we found families formerly regarded as classical hæmophilia, who were in fact suffering from a deficiency in Christmas factor and who had a normal plasma content of antihæmophilic factor. In all, we found four cases of Christmas disease or hæmophilia B. The relative incidence of the two types is shown in Table 1, together with the findings from some other reported surveys.

TABLE 1.

PROPORTION OF PATIENTS WITH HÆMOPHILIA AND CHRISTMAS DISEASE FROM PUBLISHED DATA.

	CLASSICAL HÆMOPHILIA		CHRISTMAS DISEASE
England (Biggs and Macfarlane, 1958) -	220	...	29
Switzerland - - - -	20	...	10
U.S.A. (Frick, 1954) - - -	45	...	10
Northern Ireland - - - -	39	...	4

As might be expected, the proportion of hæmophilia A to hæmophilia B in Northern Ireland is the same as that recorded by Biggs and Macfarlane for Great Britain as a whole. It is less than the proportion found in America and in Switzerland.

CLINICAL FEATURES.

The clinical features of hæmophilia are well known and we have little to add to this aspect of the disease. As the condition is a hereditary defect, which results in a predisposition to bleed readily, it is not surprising that the onset frequently occurs in early life. In the majority of cases in our series the symptoms had been present since infancy, but in a few the presenting symptoms did not occur until adult life.

The bleeding tendency was episodic, varied in severity, and had an undue frequency in the spring. It was not possible to elicit any precipitating factors, which would account satisfactorily for the clinical relapses. Many patients showed a tendency to reproduce the same hæmorrhagic pattern; some bled mainly into joints, others into muscles, and others from the renal tract. However, a combination of hæmorrhagic manifestations also occurred.

Severity of the bleeding varied from case to case and was fairly well correlated with the antihæmophilic factor level in the plasma. Mild cases were usually associated with an antihæmophilic factor level above 10 per cent. The bleeding in mild cases only followed surgical intervention or gross trauma. Five of our cases were of this type. The type of presentation in the remainder varied but the infrequency of epistaxis was notable.

Correlation between Clinical Severity and Laboratory Tests.

The correlation between the degree of clinical severity and the laboratory tests used in diagnosis do not always show a very satisfactory relationship. The tests which we will consider are the whole blood clotting time, the serum prothrombin activity, and the antihæmophilic factor level.

1. *Clotting Time.*

It is well known that this test is unsatisfactory as a diagnostic laboratory method in view of the fact that many hæmophilics have a normal clotting time (Fig. 1).

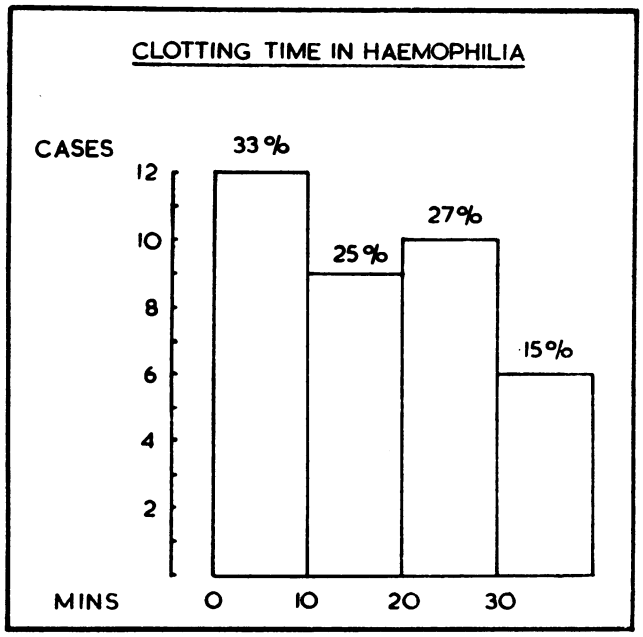

Fig 1

In general, however, it has been found that patients with a prolonged clotting time usually have severe clinical manifestations. It does not, however, follow that those with short clotting times are always mildly affected. Biggs and Macfarlane have shown that of patients with normal or slightly increased clotting times approximately half had severe clinical manifestations. Our own findings would support this. Thus a normal or short clotting time does not exclude hæmophilia nor does it guarantee a mild form of the disease.

2. *Serum Prothrombin Activity.*

This test appears to be more sensitive than the whole blood clotting time as a means of assessing deficient thromboplastin formation. However, the test may give normal results in spite of a deficiency in antihæmophilic factor. The results obtained show a fair correlation with the degree of clinical severity (Table 2.)

TABLE 2.

SERUM PROTHROMBIN ACTIVITY COMPARED WITH SEVERITY OF CASE.

SEVERITY OF DISEASE	S.P.A. % 0-20	20-40	40-60	60-80	80+
Severe	- -	–	1	1	14
Moderate	- -	2	1	3	–	–
Mild	- -	3	3	–	–	–

3. *Antihæmophilic Factor Level.*

It would seem logical that the degree of the deficiency of the specific clotting factor in the blood would correlate with the severity of the clinical manifestations. In general, this has been found to be the case.

Since the introduction of the quantitative assay method it has been shown that mild cases usually have an antihæmophilic factor level above 10 per cent., and severely affected cases a level below 5 per cent. The levels of antihæmophilic factor in seventeen of our patients are shown in Table 3 correlated with the clinical grades of severity of the disease.

TABLE 3.

ANTIHÆMOPHILIC FACTOR LEVEL COMPARED WITH SEVERITY OF CASE.

SEVERITY OF DISEASE	A.H.F. % 0-5	5-10	10-15	15+
Severe	- - 7	2	–	–
Moderate	- - 1	1	–	–
Mild	- - –	2	1	3

HEREDITARY PATTERN.

Hæmophilia is transmitted as a sex linked recessive gene and therefore the defect is located on the X chromosome. The daughter of a hæmophilic male must receive the character from her father and act as a carrier. The sons of a hæmophilic male cannot receive the abnormal gene and are thus unaffected. The hæmophilic female carrier who marries a non-hæmophilic male will bear approximately equal numbers of normal and hæmophilic sons and normal and hæmophilic-carrier daughters. A hæmophilic female carrier who marries a hæmophilic male will bear both hæmophilic sons and hæmophilic daughters. These theoretical considerations have been borne out in practice. Among humans some cases of female hæmophilics have been described, where the above criteriæ have been satisfied but they are extremely rare (Merskey, 1951; Israels, *et al.*, 1951). In hæmophilic dogs the mating of female carriers to male hæmophilic animals has produced hæmophilic female dogs (Brinkhous and Graham, 1950). Figure 2 shows the idealised pattern of hæmophilic inheritance.

In conjunction with the Department of Social Medicine we have investigated all the families of patients suffering from hæmophilia in Northern Ireland. It has been found that the family histories do not always reveal a bleeder on the maternal side. We have obtained a positive family history in 45 per cent. of our cases and in the remainder the disease appears to be sporadic. The sporadic cases may be due to non-recognition of the disease in the forebears or to spontaneous gene mutation. These findings are in conformity with those of other observers (Biggs and Macfarlane, 1958).

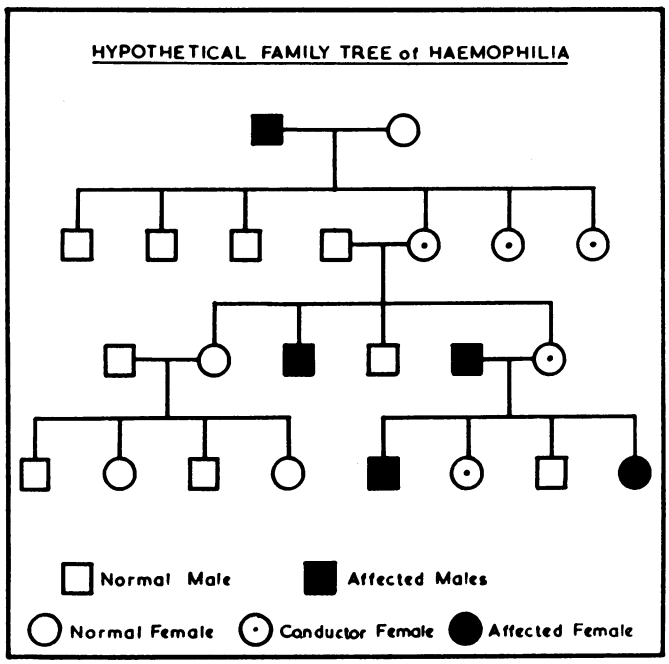

Fig 2

There is as yet no reliable way of recognising the female carrier. In our series six mothers of hæmophilic children were tested and in two a defect in anti-hæmophilic factor was demonstrated. Their alumina-absorbed plasma, when tested in a normal system, produced normal thromboplastin generation but failed to correct the abnormal generation of known hæmophilic plasma. This is to say, of six female hæmophilic carriers two had a partial antihæmophilic factor defect. Similar results have been obtained in hæmophilic carriers by Pitney (1958).

General Management.

As these patients are subject to repeated episodes of severe hæmorrhage they need to be admitted to hospital on numerous occasions. Many of these admissions are emergencies which require special management. There is, therefore, much to be said for the establishment of special centres for these patients, as has been

organised in association with the Medical Research Council. Since hæmophilia is a chronic, and in its severe form, a very disabling disease, every effort is needed to sustain morale and develop a healthy psychological approach to this life-long disorder.

It is not proposed to deal with all aspects of treatment but only with the treatment of a bleeding episode. Our experience in the management of dental extraction will be the subject of a separate communication.

Treatment of a Bleeding Episode in Classical Hæmophilia.

There have in the past been many claims put forward in support of non-plasma preparations for treatment but none have been substantiated. The only effective therapeutic preparations are fresh whole blood, fresh plasma or some specially

TABLE 4.

Effect of Fresh Plasma and Concentrated Plasma on Antihæmophilic Factor Level.

Plasma Transfusion mls.	Pre-Transfusion A.H.F. %	Post-Transfusion A.H.F. %	A.H.F. % Rise per 100 ml.	
500	1.0	7.0	1.2	
500	3.0	6.0	0.6	
750	13.0	18.0	0.66	Av. 0.84
1,000	0.5	10.0	0.95	
1,000	4.0	12.0	0.8	

Concentrated A.H.F. Actual Vol. (ml.)	Equiv. Vol. (ml.)	Pre-Transfusion A.H.F. %	Post-Transfusion A.H.F. %	A.H.F. % Rise per 100 ml.	
600	1,200	3.0	10.0	0.58	
300	600	0.8	5.0	0.70	Av. 0.73
300	600	1.2	6.8	0.93	

processed fresh plasma. It is preferable to use plasma of human origin because of its relative freedom from antigenic properties. Although animal plasma is high in antihæmophilic factor content it is strongly antigenic and consequently its use is restricted. Animal plasma has been successfully employed to tide a patient over an acute episode. Our experience has been mainly confined to the use of fresh human plasma either used immediately or stored at $-20°$ C. for not more than ten days and then allowed to thaw at room temperature prior to transfusion. We have also used the dried human plasma processed according to the technique of Kekwick and Wolf (1957) and kindly made available to us by Dr. Maycock of the Lister Institute. We have found it to be therapeutically equivalent to the volume of fresh wet plasma from which it was prepared.

The response to therapy with wet and concentrated plasma are shown in Table 4. It will be seen from this that the antihæmophilic factor rise per 100 ml. was comparable in both cases. However, the concentrated preparation has the advantage of being contained in a smaller volume.

In the past the control of hæmorrhage was frequently ineffective due to inadequate dosage. The object of plasma therapy is to raise the antihæmophilic factor content of the blood of the patient to a hæmostatic level and to maintain this level until bleeding is controlled. To achieve the first objective it is necessary to have some understanding of the antihæmophilic factor content in fresh and stored plasma, the hæmostatic level of antihæmophilic factor required and the dose of plasma needed to reach this level. To achieve the second objective some information on the survival of transfused antihæmophilic factor in the circulation is needed.

It is well known that the antihæmophilic factor is labile and therefore its concentration diminishes on storage. The factors which influence the rate of destruction are not fully understood, but there is some evidence to suggest that minor clot formation in the stored blood utilises antihæmophilic factor and therefore reduces the amount available for therapeutic use. To achieve the maximum yield of antihæmophilic factor, care in the details of collection, separation, and storage are important. The main points are:—

1. Avoid frothing during collection.
2. Use of siliconed or non-water wettable apparatus.
3. Use of citrated anticoagulant solution.
4. Careful mixing with anticoagulant during collection.
5. Separation of plasma immediately after collection of blood in a refrigerated centrifuge at 1,500 r.p.m.
6. Transfer of plasma immediately to a second cooled container.
7. Storage at $-20°$ C.

There is great variation in the levels of antihæmophilic factor among normal individuals. The antihæmophilic factor concentrations in normal plasmas may vary from about 50 to 170 per cent. of the mean (Langdell, *et al.*, 1953). The antihæmophilic factor level of a given person appears to be relatively constant. Brinkhous (1956) reported the results found in the study of antihæmophilic factor remaining in stored whole blood at $4°$ C., frozen plasma at $-20°$ C. and lyophilized plasma. From these results he concluded that after two weeks' storage whole blood retained over 50 per cent. of its initial antihæmophilic factor, whereas after three weeks only very small amounts of antihæmophilic factor remained. The deterioration in fresh frozen plasma was similar over the first two weeks but the content then remained fairly stable. In a sample tested after eighteen weeks, half of its initial activity remained. Brinkhous considers that the antihæmophilic factor content of fresh frozen plasma is approximately that of the lower limits of the normal range in an adult.

To control bleeding, Biggs considers that an antihæmophilic factor level of 30 per cent. is required. This is not always easy to achieve. Langdell, Wagner,

and Brinkhous (1955) suggested that an antihæmophilic factor concentration consistently maintained above 5 per cent. will control hæmorrhage in many instances and this has been our experience (Fig. 3). In an individual with a normal blood volume, 1,500 ml. of plasma would be required to achieve a 30 per cent. level of antihæmophilic factor or 500 ml. to raise the antihæmophilic factor to 10 per cent. In practice we give a 1,000 ml. priming dose. It is important to

A.H.F. Levels During Treatment with Plasma Transfusions of a Bleeding Episode in a Haemophilic

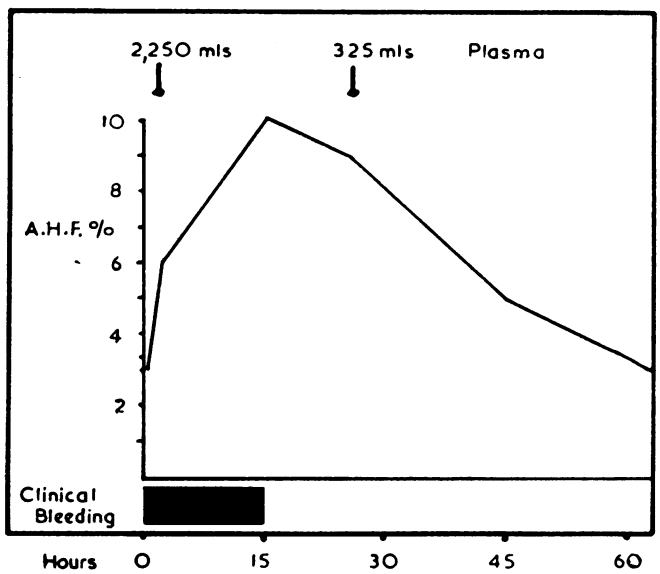

Fig 3

reach the hæmostatic level quickly, so this is given in 15-30 minutes under careful supervision. We have not produced any circulatory overload with this procedure.

The maintenance of a hæmostatic level depends on the loss of antihæmophilic factor due to tissue hæmorrhage and to decay arising from the short survival time in the circulation of the transfused antihæmophilic factor. Aggeler (1956) has shown that the half-life of antihæmophilic factor in the hæmophilic is probably less than twelve hours. However, Brinkhous, *et al.* (1956), consider that the half-life is about four hours. In the one patient in whom this was studied we found an approximate half-life of twelve hours. Because of the difficulty in determining the maintenance dose of plasma required, we have been content to use intermittent plasma therapy for our patients. We have found that the clinical hæmostatic effect of a plasma transfusion lasts twenty-four hours. Consequently we have transfused these patients at 24 or sometimes at 48-hour intervals until bleeding is controlled.

Apart from systemic therapy, all ordinary surgical precautions must be observed. In the care of wounds strict local hæmostasis by careful ligature of all bleeding points and the use of suitable antibiotics to control secondary infection should not be neglected. A useful measure in our experience in the treatment of superficial wounds has been the use of topical thrombin incorporated in an absorbable gelatin sponge.

Plasma Transfusion Reactions.

These may be due either to the presence of antibodies to antihæmophilic factor or to some other plasma protein. In several of our patients this complication of plasma transfusion has occurred. The reactions have been characterized by urticarial wheals, erythema and bronchial spasm, thus closely resembling an acute allergic reaction like serum sickness. In most cases we have found that the use of antihistamines has proved effective in controlling these symptoms. However, in severe or resistant cases we have had to give steroid hormones in addition.

Christmas Disease.

From the standpoint of hereditary transmission and hæmorrhagic manifestations this bleeding disorder resembles classical hæmophilia. Unlike classical hæmophilia, there is no deficiency of antihæmophilic factor. Plasma from these patients corrects the clotting defect of hæmophilic patients both *in vitro* and *in vivo*. This disease is due to the deficiency of a factor called Christmas factor, which is activated during the coagulation of blood and can be demonstrated in serum after clotting occurs.

The routine laboratory tests in Christmas disease are similar to those in classical hæmophilia. The clotting time may be normal or prolonged. The prothrombin time is normal. The prothrombin consumption may or may not be abnormal. The thromboplastin generation test will demonstrate a normal concentration of anti-hæmophilic factor in the plasma and will detect a deficiency of Christmas factor in the serum. The introduction of this test has allowed the clear separation of classical hæmophilia from Christmas disease.

In this survey only four cases of Christmas disease were seen as compared with thirty-nine cases of classical hæmophilia. In three of the four cases there was a characteristic hereditary pattern of classical hæmophilic type. From the clinical point of view there is a belief that Christmas disease is a less severe form of bleeding disorder. This is not so. Along with others we have found severe and mild forms of both classical hæmophilia and Christmas disease. Two of our four cases of Christmas disease exhibited severe clinical manifestations of bleeding. Furthermore, the brother of one of these latter patients was seen by one of us before the present investigation started. He was known to be a bleeder, had been diagnosed as hæmophilia, and died following a gross hæmorrhage into the psoas muscle. The laboratory findings and the clinical manifestations in our surviving cases are presented in Table 5.

Management of a Bleeding Episode.

Cases of Christmas disease show a satisfactory clinical response to transfusions of both blood and plasma. In this respect they behave like hæmophilia. However,

TABLE 5.

FINDINGS IN CHRISTMAS DISEASE.

No.	CLINICAL MANIFESTATIONS	CLOTTING TIME	SERUM PROTHROMBIN ACTIVITY
1	Mild—easy bruising	Normal— 6 mins.	Normal
2	Mild—easy bruising and hæmaturia	Normal—10 mins.	Normal
3	Severe—bruising, melæna, hæmarthroses, retro-peritoneal hæmorrhage	30 mins. +	Abnormal
4	Severe—bruising and hæmarthroses	30 mins. +	Abnormal

Christmas factor is more stable than antihæmophilic factor. As it is not used during coagulation, it is found in blood serum. Furthermore, it is claimed that Christmas factor, when transfused into a patient, has a long half-life and may remain in the circulation for two to three weeks (Beaumont, *et al.*, 1954). For these reasons, the management of a bleeding episode is much simpler in Christmas disease than in classical hæmophilia. Although our clinical experience of the treatment of Christmas disease has been limited, we have noted the ease with which plasma transfusions have controlled bleeding episodes. As the Christmas factor is stable, it is possible to use either plasma or serum for transfusion. It must be remembered, however, that serum is of no value in the treatment of classical hæmophilia and therefore accurate diagnosis is essential before such therapy is used in 'hæmophilia.' We have used plasma from bank blood stored at 4° C. for not more than twenty-one days and found it to be therapeutically effective in Christmas disease. A single transfusion of as little as 1,000 mls. caused immediate and permanent cessation of clinical bleeding, maintenance therapy not being required.

SUMMARY.

A survey has been made of hæmophilia in Northern Ireland. Thirty-nine cases of classical hæmophilia have been found in the population in this area, giving an incidence of one in 45,000. A study of the hereditary pattern has revealed a positive family history in 45 per cent. of our cases.

The value of laboratory tests in the diagnosis of hæmophilia was studied. On the tests used the clotting time was found to be least valuable, being normal in one-third of the cases. The serum prothrombin activity was a more useful diagnostic test but the most valuable was the thromboplastin generation test. A modification of this test allows a quantitative estimation of the antihæmophilic factor in the plasma to be made.

The clinical severity of the cases was found to correlate with the level of antihæmophilic factor in the plasma. Mild cases had a level above 10 per cent. and severe cases a level below 5 per cent.

The management of bleeding episodes in classical hæmophilia is described. The importance of rapid and adequate plasma transfusion to attain a hæmostatic level of antihæmophilic factor is stressed.

Four cases of Christmas disease have also been studied and a positive family history obtained in three of these. The hereditary pattern and clinical manifestations were identical with classical hæmophilia. Differential diagnosis can only be established using the thromboplastin generation test. The management of bleeding episodes in Christmas disease is described. The relative ease in controlling hæmorrhage, even with small plasma transfusions, is pointed out. Christmas disease can also be successfully treated by transfusion of serum. Because of this it is important to establish an accurate diagnosis between these two conditions before therapy is applied.

ACKNOWLEDGMENTS.

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THE GYNÆCOLOGIST AND THE LAW

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BASED ON PART OF A PRESIDENTIAL ADDRESS
to the Ulster Obstetrical and Gynæcological Society on 20th March, 1958

Professional Negligence.

During the early years of the Health Service damages awarded in the courts for negligence increased to an alarming degree. There were at least three factors contributing to this state of affairs—the introduction of free legal aid, certain changes in the law relating to the liabilities of hospitals for the negligence of their staffs, and a perhaps understandable view by the general public that damages were now coming "off a broad back." Since 1953, however, it seems to have become less easy to recover damages; there have been a number of judicial opinions expressed recently which are encouraging to the medical profession, to the effect that a doctor should not be held liable for negligence merely because some mishap occurs.

Professional negligence can be defined in a number of different ways, but a simple definition is failure to exercise a reasonable degree of skill and care during the treatment of a patient. The law imposes on certain persons a duty to take care, and a doctor is one of them; once he undertakes the responsibility of treating a patient he assumes "a duty of care," and in law he will be expected to attain the standard of a reasonably skilful and careful member of his profession. Most cases will be judged on their own merits. For instance, a consultant practising in his own speciality will be held liable for negligence in respect of treatment which in a general practitioner or a junior member of the profession might be regarded as quite satisfactory; his standards must be those of a reasonably skilful and careful consultant.

It also seems fairly definite that all doctors, and particularly those who specialise, will be expected to keep abreast of modern developments and new techniques. It is unlikely that any one of us will be liable if damage could have been averted only after reading a particular article in a medical journal, but we would be expected to know, for example, if a drug or clinical method had been tried out and found to carry special dangers or disadvantages. We are, of course, entitled to adopt our own methods of treatment even if they do not meet with universal approval, so long as they are approved by a substantial proportion of our colleagues and are carried out with reasonable skill and care.

What of the cases in which we fail? In parts of the United Kingdom the general public seem to have reached the point where they feel that to be treated

in hospital is to have a cure guaranteed—a subtle form of flattery, perhaps, but very disturbing if it should ever reach the stage (as it is reported to have in parts of the U.S.A.) where failure to diagnose twins or deliver successfully a breech might lead to litigation. I sometimes wonder whether we ourselves are not to some extent to blame when a patient is dissatisfied with the results of the treatment; a little more time spent in explaining that a proposed operation or line of treatment will not necessarily cure or even relieve her symptoms is usually time well spent. But there are some grains of comfort for us in the pertinent if rather highly coloured observations on this subject made a few years ago by Lord Justice Denning[1]:—

> "I ought to tell you what the law is on this matter of negligence against doctors and hospitals. On the roads or in a factory there ought not to be any accidents if everyone uses proper care, but in a hospital, no matter what care you use, there is always some risk. Every surgical operation involves risk. It would be wrong, and indeed bad law, to say that simply because a misadventure or mishap occurred, thereby the hospital and the doctors are liable. Negligence against a doctor is for him like unto a dagger. His professional reputation is as dear to him as his body, perhaps more so, and an action for negligence can wound his reputation as severely as a dagger can his body. You must not, therefore, find him negligent simply because something happens to go wrong, as, for instance, if one of the risks inherent in an operation actually takes place or because some complications ensue which lessen or take away the benefits that were hoped for, or because in a matter of opinion he makes an error of judgement. You should only find him guilty of negligence when he falls short of the standard of a reasonably skilful medical man. In short, when he is deserving of censure—for negligence in a medical man is deserving of censure."

Certain changes have recently been made in the law concerning the liability of hospitals for their medical staffs. Before the Health Service Act was passed it was generally accepted that the only duty undertaken by the governors of public hospitals towards a patient was to use due care in selecting their medical staffs. The relationship of master and servant did not exist between the governors and the physicians and surgeons who gave their services at the hospitals. Nurses and others when assisting at operations ceased for the time being to be the servants of the governors; they took their orders during that period from the surgeon alone, and only very occasionally was a nurse held liable for anything which went wrong. This principle was established as long ago as 1909 in a case which involved St. Bartholomew's Hospital.[2]

More recently there has been quite a marked change in this aspect of the law, and the first milestone was probably the case of Gold v. Essex County Council in 1942.[3] In this case a competent radiographer was found to have been professionally negligent. He was at the time a whole-time employee of the hospital, and the management committee, as his employers, were held to be liable for his negligence even when he was engaged on work which involved the exercise of professional skill.

This decision was extended in 1951 to apply also to doctors and surgeons.[4] It was held that liability must depend on who employs the doctor or surgeon. If the patient himself selects or employs the doctor or surgeon the hospital

authority cannot be held liable for his negligence because he is not employed by it. But where the doctor or surgeon, be he a consultant or not, is employed and paid not by the patient but by the hospital authority, then the authority may be liable for his negligence in treating the patient.

There is certainly no longer any question that the employing authority is responsible for the acts of their resident medical staff. But so far as part-time consultants are concerned there is probably still an element of doubt about the position; it is possible that some distinction will still be drawn, as it was in the past, between contracts for service (i.e., consultants) and contracts of service (i.e., house officers). However, the trend of legal decision recently seems to indicate quite clearly that the doctrine of vicarious responsibility[5] (responsibility delegated by the employing authority) will also be applied to consultants, whether part-time or whole-time. It is interesting to note how the attitude of the Ministry of Health in London has already changed. About 1952 Regional Boards were instructed by the Ministry not to undertake the legal defence of any member of their medical staffs involved in a legal action. If it seemed likely that a hospital would be involved in the alleged negligence of a doctor the Boards were advised to bring the doctor into the action in order to obtain a contribution from him in respect of any damages awarded. Two years later the Medical Defence Union, in concert with other protection societies and the British Medical Association, were able to reach agreement with the Ministry and so bring the system to an end. In a recent report[6] the Medical Defence Union say that this has been a great step forward because it has resulted in a more frequent presentation of a united front by hospital authorities and the protection societies; and that it has gone some way towards eliminating the feeling that lay administrators seem more concerned with "passing the buck" or in settling out of court than in contesting unjustifiable claims. The obvious danger in this arrangement, to which attention was drawn at the time, is that in cases where the hospital authority alone is sued and the conduct of the defence left to the authority the interests of the medical men concerned may be insufficiently considered. So far, however, the Medical Defence Union feel that this has not happened.

Another possible consequence which still causes a good deal of concern in Scotland (where the law is slightly different) is that if a court rules that a consultant is the "servant" of the hospital authority, this may lead to various undesirable sequelæ such as the issue of clinical directives. In fact, what the courts have so far held is that we are "agents" or "delegates" but not servants. Furthermore, it seems that these words have little exact meaning in law and contain no implication of any power to dictate on clinical matters. Indeed, in one of the judgements[7] made about three years ago it was stated quite clearly that, in the view of the court, it is not open to a hospital authority to do any such thing, even if it were so desired.

Consent for Operation.

In gynæcological practice it is not uncommon to be confronted by a patient requesting sterilisation. There seems little doubt that if there is a good medical

indication the matter is simple, because it is akin to therapeutic abortion. But if the sole reason is that the couple wish to avoid having any more children the legality of sterilisation is much more doubtful. Karminski and Reeve[8] state that they are aware of no authority to support the view that it is illegal provided the usual safeguards of written consent from both husband and wife are obtained. On the other hand, just a few years ago the medical protection societies[9] thought it advisable to obtain a fresh opinion from counsel on the matter, and this was given to the effect that sterilisation on eugenic grounds alone is illegal, and I suspect that this would include purely social and domestic issues also; it is not so if there are valid therapeutic reasons and a second opinion is obtained. Some of us at one time or another, when faced by a husband adamant that his wife should be sterilised, may have taken refuge in the time-honoured suggestion that it would be much easier if he were sterilised. This approach to the problem will sometimes have its salutary effect, but in fact sterilisation of the husband is of very doubtful legality even when supported by the full consent of both parties concerned unless it is performed for some specific indication such as insanity.

Perhaps the most difficult decisions relating to consent are those which arise during laparotomy, often quite unexpectedly. We may well wonder to what extent we are free to use our discretion regarding the removal of tubes, ovaries, and the uterus, and to what extent the usual consent form signed before laparotomy gives us complete carte-blanche to do what seems best. Before the days of the Health Service it may have been quite reasonable to believe that if a patient came to hospital either on her doctor's advice or on her own initiative she was deemed to agree to receive treatment, but unfortunately this cannot be said to hold good in law today.[10] Consent must be "full, free, and valid in all respects." To secure it we must make known to the patient what we propose to do and what the possible consequences are—often no easy matter to put into words. There is at least one interesting example of the type of legal tangle in which we can find ourselves unless we are very careful[11]:—

> This was the case of a patient on whom a bilateral oophorectomy was performed. She alleged that she had expressly forbidden the removal of both ovaries, although she had consented to the removal of one of them. The case was in the end contested successfully, but not so very easily, on the grounds that the operation had been left to the gynæcologist's discretion, based on the results of exploration; that the double oophorectomy was necessary in order to prolong the patient's life, if not to enable her to escape imminent danger; and that the cause of her sterility was not the operation but the cystic condition of the ovaries at and preceding operation.

Legal opinion stresses the importance of having a clear statement that the scope of the operation will be left to the discretion of the surgeon after he has gained full information. The subject is dealt with in some detail by Taylor,[12] who goes so far as to state that if a surgeon finds he must exceed the limits of pre-operative permission he should consult with the nearest relative or else be able to rely on the extreme necessity of the case before proceeding. As always, the value of a second opinion is emphasised. In our Ulster provincial hospitals another gynæcological opinion is seldom less than thirty miles away; when in doubt I

have had the greatest help from our consultant anæsthetists—and as onlookers who see perhaps most of the surgical game one can scarcely doubt that their opinions would count as much in law as in every-day practice.

Biopsy Diagnosis.

It is surprising to find little reference in writings on the subject of negligence to the support which I believe we can also get from our pathologists. While in Canada recently I was impressed by the emphasis placed on the routine pathological examination of all tissues removed at operation; indeed it was an absolute rule in most hospitals. There is no doubt that some of this insistence came from "Tissue Committees" intent on reducing unnecessary surgery, but there was a medico-legal motive as well. The taking of vaginal smears for cytological examination as a matter of "office routine" was also stressed as being a sensible precaution because it seems that the stage has now been reached in some parts of the U.S.A. at which, if an early uterine cancer is missed, failure to have taken a smear can be construed as negligence.

Failure to take a biopsy has, of course, been the subject of litigation in England, and it is interesting to recall the details of two such cases[13]:—

> One of these concerned a hysterectomy performed by a woman gynæcologist, the patient being a doctor. Some time after the operation the patient's marriage broke up and she attributed this to the hysterectomy which she claimed had been unnecessary. It seems that the gynæcologist had carried out diagnostic curettage, considered the endometrium on macroscopic examination to be malignant, and had proceeded with the hysterectomy. Subsequent histological examination showed that the endometrium was not in fact malignant. The gynæcologist eventually won the case. She contended that her colleague had asked her to use her discretion and proceed with hysterectomy if the curettings appeared suspicious, rather than subject her to a second anæsthetic.
>
> The other case is also well known. An American businessman, while in England in 1942, developed acute urinary retention. The surgeon, after opening the bladder, found, on careful manual and visual examination, what he concluded was an inoperable prostatic cancer. The patient was told the exact diagnosis so that he could return to America and settle his affairs. There it was found that the mass in question was not malignant, and it was in fact removed successfully.
>
> An action was brought for negligence, one of the grounds being the surgeon's failure to take a specimen of the presumed carcinoma for biopsy. Mr. Justice Birkett held that the surgeon had been negligent in not making a microscopical examination, and that he had been lacking in his duty in taking no step to check or verify his diagnosis. Judgement was entered against the surgeon for the sum of £6,300. On appeal, Mr. Justice Askwith held that a doctor was not liable in negligence by reason only that he made a mistake in diagnosis. The surgeon had maintained that his failure to take a biopsy had been a deliberate decision after prolonged thought, that to have taken a biopsy would have carried some risk, and that what he had done had been in accordance with established medical practice. He was cleared completely of negligence and no damages were awarded; but we should perhaps remember that this case was heard sixteen years ago and it might now be much more difficult to substantiate failure to take a biopsy from any organ if there were the slightest suspicion that it might be malignant.

While preparing this address I frequently felt I was very much the amateur trying to interpret the work of professionals; my object has been to stimulate your interest without, I trust, giving the impression that I am in any way an

expert. British law has always been "the legislative expression of public opinion" and as such it is never static; its complexities are in the long run best left to those who profess to be experts.

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COMBINED INTERNAL CEPHALIC VERSION

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CEPHALIC version is the manipulation by which the presentation is altered to make the head lie over the brim of the pelvis. Most doctors are familiar with external cephalic version. Internal cephalic version is a bipolar version performed by the whole hand inserted through the cervix of the anæthetized patient, aided by the other hand on the abdomen and this, to judge by current text-books, is a manœuvre which many obstetricians, even the most experienced, ignore. Bipolar is used in its literal sense to indicate a manœuvre performed by pressure on both poles of the fœtus, the pressure on the lower pole being exerted by the whole hand and not by two fingers as was implied in earlier times by the use of this terminology and which meaning is still often read into the expression.

Kerr and Moir (1949) state, "Internal cephalic version, the operation of Hippocrates, has practically been given up." Stander (1936) writes, "Cephalic version may be accomplished by the combined or bipolar method of Braxton Hicks as soon as the cervix is sufficiently dilated to admit two fingers. It, however, is rarely employed as, in such circumstances, it is usually advisable to wait until the cervix is fully dilated and then to rupture the membranes and do a podalic version followed by extraction." He does not mention a cephalic version, using the whole hand inside the uterus. Few authors are as dogmatic as Eastman (1950): "Cephalic version in modern obstetrics is performed solely by external manipulations." Stern and Burnett (1952) state, "Bipolar version is usually podalic." Referring to internal version they write, "When the cervix is three-fifths or more dilated, the whole hand may be introduced into the uterus. Version is performed by seizing a foot and pulling it down through the cervix, the other hand assisting by abdominal manipulation." Internal cephalic version is not discussed. Strachan (1947) merely defines the manœuvre. Brews (1948), while mentioning that earlier records show that internal version was used to bring down the head, states, "Within recent times it has been employed only as a method of podalic version." Gibberd (1955) completely ignores the possibility of internal cephalic version. Baird (1953) states, "Although originally cephalic version was employed, podalic version is now more common as the foot is much easier to grasp than the head."

One feels, however, that internal cephalic version has a definite place in the treatment of some cases of oblique lie, despite the scanty and, as has been seen, often scathing references to the manœuvre in current literature. Modern text-books should at least mention, in the treatment of transverse lie, this operation as one which occasionally might well be the method of choice.

Recently five infants in this area, four in Daisy Hill Hospital, Newry, were delivered by this manœuvre, two within a few hours of one another. The cases

of twin pregnancy are reported for illustration only, since in this hospital in the operative delivery of a second twin, lying obliquely, internal cephalic version followed by forceps delivery is used almost as frequently as internal podalic version and breech extraction.

Case Reports.

Case 1. A multipara at 38 weeks maturity had had spontaneous delivery of a first twin. Twenty minutes later she developed a sudden intrapartum hæmorrhage of about one pint (560 c.c's.). Abdominal examination at this stage was not satisfactory presumably because the first placenta intervened between the palpating hands and the second fœtus. Vaginal examination revealed a limb through the bag of waters. It could not be clearly identified. Since by manipulation through the intact membranes the lie could not with certainty be rendered longitudinal, the membranes were ruptured. A hand prolapsed. The head was felt in the right iliac fossa. It was drawn over the pelvis and flexed in the right occipito anterior position. The prolapsed arm was replaced, following which, with the aid of strong fundal pressure, the head was guided into the pelvis and a high mid cavity forceps operation was performed. Light traction only was required to deliver a living male infant which weighed 5 pounds 1 ounce (2292 G).

Case 2. A seventh para with a previous normal obstetric history was an emergency admission because of concealed accidental hæmorrhage in the thirty-seventh week. The uterus was extremely tense, making it impossible to define the presenting part. The fœtal heart rate had been about 60 before admission but in hospital was inaudible. X-ray revealed the fœtus to be lying transversely with its head in the right iliac fossa and the back presenting. About one hour following admission, vaginal bleeding occurred and about three pints of blood were rapidly lost. Transfusion of two pints (1136 ml.) compatible blood and two pints (1136 ml.) glucose saline restored the blood pressure to 130/80. Uterine contractions continued to increase in strength and frequency and six hours later the patient stated she felt like bearing down with her pains.

Examination under anæsthesia confirmed the X-ray findings. There was a loose flap of cervix present. It was felt that it was unlikely that the cervix would dilate any further. Arrangements had been made to do a decapitation. Before this, however, a hand was passed easily round the fœtal head and very moderate tension only was required to bring it over the brim of the pelvis. It was flexed and rotated into the occipito anterior position and forceps applied. Light traction delivered a fresh still-born infant weighing 7 pounds 15 ounces (3594 G). This manœuvre occupied about five minutes and necessitated the minimum of trauma both to patient and operator. Internal podalic version, with the infant lying as it was, might well have been dangerous. Decapitation, the other alternative, is an operation which causes an appreciable degree of psychic trauma to the nursing staff and on occasions physical damage to the patient.

Case 3. This patient, also a seventh para, had had a transverse lie corrected on many occasions during the pregnancy. She was admitted in labour in the forty-first week and again had to have the lie righted. Seven hours later the malpresentation recurred and the fœtal heart was becoming irregular. Strong

pains were occurring every four minutes. The membranes were still intact. The fœtal head lay in the right iliac fossa and a new and unusual feature had made its appearance. There was a swelling the size of a grapefruit above the symphysis and occupying the position of the distended and drawn-up bladder, often seen in obstructed labour. Catheterization proved that the bladder was empty. Examination under anæthesia showed that the swelling was a cervical fibroid the shape of a half-sphere, of diameter about 3″ (7.6 cm.), with its base centred over the anterior part of the lower segment and projecting slightly into the uterine cavity. The os was about three-quarters dilated. Nothing could be clearly defined through the bag of membranes. At this stage, however, the waters broke with the discharge of about three pints (1700 ml.) of meconium-stained liquor and very numerous coils of umbilical cord. Following rupture of the membranes the intrauterine projection of the base of the fibroid became more pronounced. The head was drawn over the pelvis and an attempt made to replace the cord above it. Even with the help of gravity this manœuvre proved hopeless. The pulsations of the cord numbered only about twenty per minute. Since the fibroid had been pulled above the level of the brim of the pelvis and as the patient had a good obstetrical history, it was decided to attempt a high forceps operation in the interest of the fœtus. With the help of fundal pressure the vertex was steadied in the left occipito anterior position. The presence of the fibroid held it almost entirely above the pelvic brim. Barnes-Neville forceps were applied with proper regard to the position of the head. Several loops of cord, perforce, were caught between the blades and the fœtal skull. Easy traction delivered a live male infant with slow heart beat which, however, gasped in about twenty seconds and whose further progress was uneventful. It weighed 6 pounds 14 ounces (3113 G) at birth.

The alternatives were Cæsarean section and internal podalic version. By the time the theatre would have been ready, one feels the infant would have been dead. With regard to internal podalic version, in this case, because of the number of prolapsed loops of cord and the presence of the large fibroid, any intrauterine manipulation would certainly have necessitated compression of one or more coils of cord and had the procedure been prolonged, almost certainly would have caused the death of the fœtus. In any event, internal version would not have been easy because the legs were not readily available.

Case 4. This patient had had two previous spontaneous normal deliveries. She was admitted as a twin pregnancy with premature rupture of the membranes in the thirty-fifth week and had easy, spontaneous delivery of the first twin after a labour of only one and a half hours. When seen in consultation one hour later the second infant was found to be lying obliquely with the presenting part very high. A sausage-shaped bag of membranes was present. This was ruptured and the infant's head drawn over the pelvis. The fœtus was tightly gripped by the uterus and held at a very high level and the lie could not be stabilized longitudinally. The most advanced part of the vertex was calculated to be about 2″ (5.0 cm.) above the level of the pelvic brim. Strong fundal pressure by two nurses caused the head to advance until the greatest diameter was approximately

1″ (2.5 cm.) above the level of the inlet. It was lying in the right occipito anterior position. High forceps were applied with a cephalic grip. Firm but not strong traction was required to deliver a healthy male child which weighed 5 pounds 14 ounces (2661 G).

Case 5. Another twin pregnancy at term had delivered the first infant spontaneously, this time in a hospital some thirteen miles away. Two hours later the patient's own doctor ruptured the membranes of the second sac only to be presented with an arm. On arrival half an hour later one found the fœtal heart rate was slow. Strong pains were occurring every three minutes. The head was to the left side of the mother's abdomen. With firm, controlled pressure by the internal examining hand the shoulder was disimpacted and the head induced over, and into the pelvis. A low mid-cavity forceps produced a healthy infant to the gratification of all, and the amazement of the general practitioner at the apparent ease and simplicity of the whole procedure.

Indications.

The indications for internal cephalic version are the same as those for internal podalic version followed by breech extraction provided that neither has any place in the treatment of contracted pelvis, and in primigravidæ internal version is a manœuvre of very doubtful wisdom except with multiple pregnancy. In the writer's hands the most common indication is in the operative delivery of a second twin whose lie is not longitudinal. The second most common indication is the transverse lie, in a multipara with a good pelvis, which has not righted itself or cannot be righted by other means, by the time of full dilatation of the cervix. An easy internal cephalic version may be the alternative to a difficult breech extraction. In other cases, however, the operation may be impossible.

Conditions.

The cervix must be sufficiently dilated to allow of subsequent delivery. Especially in shoulder presentation, however, the os often does not become fully dilated but under anæsthesia is found to stretch easily without any tendency to tear. There must be no disproportion. When the uterus is on the point of rupture or the child tightly gripped by the lower segment internal version should not be employed. Considerable experience and judgment are required to evaluate these factors. If the child is dead, unless version promises to be exceptionally easy, some other method of delivery should normally be used.

Choice of Operation.

Internal version being indicated, the decision as to whether to do a podalic or a cephalic version is simple—one does the easier. A straight X-ray of the abdomen often helps. Many transverse lies are really oblique and if the head is nearer the fundus than the os, then probably it would be easier to bring down the legs. As a rule in a pure transverse lie, if the back is presenting, cephalic version is the easier, while if the back is uppermost it again will probably be easier to bring down the legs. An important consideration, however, is the attitude of the cervical spine. These facts are rapidly ascertained on vaginal examination if no X-rays are available.

Technique.

If the head is to the operator's left, the left hand is inserted into the uterus and vice versa. All internal manipulations are aided by pressure from the other hand on the abdominal wall. The amount of force should be minimal. The head should be led to the brim of the pelvis and flexed with the occiput to the front. An assistant is required who, by fundal pressure, forces the head into the pelvis as the internal guiding hand is withdrawn. If the case has been chosen properly and there is no disproportion the head can usually be made to advance until the greatest diameter is in or through the brim of the pelvis. On occasions, however, as in two of the illustrated cases, this may not occur. In such cases, properly chosen and with an experienced operator, a high forceps application is quite in order.

Summary.

A review of current text-books reveals an almost total neglect of the operation of internal cephalic version. Five cases recently treated within a short time of one another by this method are presented in order to support a claim that the manœuvre has a place in modern obstetrics and should be revived. When the necessity for internal version arises, one should not automatically proceed to internal podalic version—one should consider the possibility of internal cephalic version and perform whichever manœuvre is the easier and so less traumatic to both mother and fœtus. Internal cephalic version may proceed to a high forceps delivery if fundal pressure does not leave the head in the pelvic cavity. This operation, *per se*, is rightly condemned, but for the experienced obstetrician, if the case be chosen carefully, the operation still has a place.

The indications, conditions, and technique of internal cephalic version are described.

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SOME ASPECTS OF THE RELATIONSHIP BETWEEN MOTHER AND CHILD

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I MUST, at once, say what a pleasure it is to see so many old friends again, and I must thank most warmly those who have put me into my present privileged position. Effectively to recapture the past is beyond most of us. The attempt by an individual to do so, however, can be pleasurable and may be salutary or even poignant. But be the reaction as it may, the evocation of old and partly forgotten experience is sometimes a pious duty—as it is for me on this occasion.

I joined the medical school here, in the company of several who are also present tonight, nearly thirty-five years ago. Since I left Belfast, after having been successively student, houseman at the Royal, and demonstrator of anatomy, a quarter of a century has elapsed. My memories of this medical school, therefore, which are very happy ones, go back a long way, encompass a considerable period, and, in some respects, are remarkably clear. If the occasion were opportune what tales I could relate, and not only of my fellow-undergraduates!

Unfortunately these memories, in the context of tonight's commemoration, do not go back far enough for me to give you a first-hand and coherent account of Robert Campbell. His name was held in the highest regard by our clinical teachers, who had been his colleagues and pupils. And to this vicarious knowledge of him I can add one piece of direct evidence on the manner of man he was. My father-in-law, who knew him well, used to tell of sitting beside him in a tram. Robert Campbell suddenly emerged from a small volume in which he was immersed to exclaim—"There's the best definition of life I have met!" The book was *Measure for Measure*; the line indicated was "*This sensible warm motion*"—from Claudio's moving speech in the first scene of the third act. Such an anecdote, trivial though it may seem, surely limns the character! He was a successful, and busy, surgeon who read Shakespeare in a tram-car, and read him with critical and sensitive attention. Of Robert Campbell's high standing in his profession you will have been told in previous orations, made by those better able, by far, to judge on such a matter than can I. Nevertheless, I must record that I have heard high praise of him, and of his work—as a pioneer in aseptic surgery, as first in the diagnosis of the obstructed appendix, as brilliant innovator in the repair of infantile herniæ. And I have heard this praise in regions where it was not underwritten by local patriotism. Robert Campbell was one of that distinguished group of Belfastmen who put the Queen's Medical Faculty on the

right road to its achieved, and present, high distinction. It is meet that he should be remembered here. I have been so long dissociated from active contact with clinical medicine that I feel myself peculiarly inappropriate as the commemorating orator. Nevertheless, it is possible that Robert Campbell would have been pleased that, like him, I was once a demonstrator in anatomy at Queen's. And as he had such a deep interest in the surgery of childhood it is even possible that he would have been interested in, at least, the subject I am committed to discussing.

None of you will expect from me a complete exposition of the relationship between mother and child. Such an exposition would, patently, be far beyond my competence. I am an anatomist, by trade and, indeed, by inclination. What I shall have to say will, therefore, relate primarily to structure, though, I hope, in the idiom of contemporary anatomy. I am sure you all must know that the climate of opinion in anatomy has undergone a revolutionary change in our lifetimes, and that it is now fully intercalated into the advancing front of contemporary biology. So if, from time to time, I leave the details of structure to consider their general implications, I shall not be exceeding what modern anatomists consider to be their duty.

For many years, both alone and in collaboration, I have had a continuing interest in the mammalian placenta. This most remarkable transient organ is, of course, the *sine qua non* in the fœtal-maternal relationship. Considering its basic importance, it is surprising how ignorant we remain about many fundamentally important aspects of its structure and function. I shall, perforce, have to restrict myself now to the human placenta, and, indeed, to certain particular aspects of it to which I have been able to give direct attention.

But, firstly, may I briefly orientate you on the basic structure and relations of the placenta (Pl. I, Figs. 1 and 2). Such an orientation requires a summary account of its origin for it is by knowing how structures arise that we can understand how they come to acquire the features they possess. The human zygote enters the uterine cavity as a blastocyst and, as the classical investigations of Hertig and Rock (1956, for summary) have shown, implants there during the seventh day after ovulation. At this time the endometrium is in the luteal phase of the uterine cycle. The uterus has been 'primed' for the reception of the blastocyst. Its lining is markedly thickened and its glands are much enlarged, tortuous, and full of secretion. The exact nature of the glandular secretion has yet to be determined, but we know that it contains lipids, protein (especially muco-protein) and glycogen. It possibly also possesses some lyzozyme-like quality which renders it bacteriostatic. There are a very large number of the endometrial glands, according to my own computations, not fewer than 15,000 of them. Their secretion presumably supplies an optimum background for the unimplanted blastocyst when it is lying free in the uterine lumen. The blastocyst becomes attached between the mouths of several of these active glands and rapidly makes its way through the mucosal epithelium so that soon, by the eleventh or twelfth post-ovulational day, it is completely implanted in the maternal tissues. The mechanism by which such interstitial implantation is effected is not well understood. In particular the precise rôles of egg and

endometrium in the process are unknown. The implanting blastocyst wall, or trophoblast, may produce a cytolytic enzyme which is responsible for the epithelial erosion at the point of contact, though there is no direct evidence available to establish this probability. From animal experiments, it is known that the uterine mucosa can embed inert objects. Every ectopic gestation demonstrates that implantation can take place other than in the uterus. To assign quite separate rôles to the conceptus and to the maternal tissues in the process is probably an over-simplification, for it is a mutual and remarkably tolerant relationship which is established. And to this tolerance I should like, for a moment, to direct your attention.

A fact of basic significance in the maternal-fœtal relationship is that (apart from animal strains so inbred that all their members are essentially homozygous) the genetic structure of mother and offspring is different. This, of course, is the reason why, in post-natal life, a skin graft from one to the other, in either direction, will not "take." Such a graft, like most other homografts, induces a reaction in the host whereby its immunological, anti-foreign protein resources are mobilised. Consequently, after a brief interval, the graft will be destroyed. The work of Medawar (1958) has shown that soluble antibodies are unlikely to be primarily concerned in effecting this destruction. Rather it is cells of the host's reticulo-endothelial system which are sensitized by the presence of products of the graft. Such sensitized cells are discharged into the blood stream and pass with it to the site of the graft and, once there, proceed to cast off the alien cells. Certain tissues, however, notably the cornea, cartilage, and the fibrous framework of arteries, can be successfully grafted. Whether this lack of susceptibility on the part of these privileged tissues is due to the absence in them of a vascular supply (as seems most likely); or to insulation and protection by the muco-polysaccharide of their matrices; or to absence of, or absence of liberation of, antigen is not altogether clear, and need not, here, be explored further. The point that must be made is that neither in the early stages, nor, indeed, at any stage in pregnancy, does the trophoblast of the placenta appear to behave as a sensitive or sensitizing homograft. That it is, in fact, a homograft there can be no doubt. Moreover the trophoblast is in most intimate contact, indeed, in direct contact, with the maternal blood in the intervillous space. Separated portions of it may come to lie in the depths of the endometrium, well away from the placental site and even in the myometrium (Pl. II, Figs. 3 and 4), yet I have never seen such trophoblast to induce such a reaction in the maternal tissues as is to be expected from its genetic structure. Even more curious, though the phenomenon is well established, small fragments, the so-called syncytial sprouts, of the trophoblast are continuously being discharged into the maternal circulation. They pass to the mother's lungs (Schmorl, 1893; Park, 1958), just as do the more spectacular metastases of chorio-epithelioma, where, however, they seem to undergo cytolysis. I have seen such syncytial sprouts in sections through uterine veins remote from the placenta (Pl. II, Figs. 5, 6, and 7), and my friend, Dr. Lewis Thomas, of Bellevue Hospital in New York, informs me that he has found them in blood removed from uterine veins during hysterotomy or Cæsarian section.

The absence of a homograft reaction to trophoblast on the part of the maternal organism is the more remarkable in view of the well-known formation of maternal hæmolysing antibodies to fœtal blood when the latter possesses certain special antigenic properties. Moreover, the tissues of the fœtus itself do not, at least in the rabbit, appear to possess significant protection against maternal antibodies (Woodruff, 1958). The notion of the placenta as a homograft is recent, but I hazard the opinion that, progressively, much more will be heard of the problems such as concept poses. In particular, it is important to establish whether the absence of a homograft reaction by the maternal organism to the embryonic trophoblast is complete or not. If the absence of response is only relative and can vary in any way with the genotypes involved certain puzzling problems in gestation and fertility may receive their explanation.

Well, then, the blastocyst becomes implanted in a prepared endometrium and is not treated there as our knowledge of homografts would lead us to expect. But if there is no immunological reaction to the trophoblast there is a most obvious local mechanical effect of the presence of the conceptus. The uterine glands are pushed aside—elbowed out of the way, as it were—by the enlarging chorionic tissue. Many glands are eroded by the trophoblast, and their secretions come into direct contact with it. This erosion of the glands continues for a long period, certainly until the end of the second month of gestation. Moreover, owing to the breakdown of the distal parts of the glands, secretion from them comes into direct contact with the trophoblast and, indeed, can pass directly into the intervillous space (I.V.S.) or into gaps, between the trophoblastic cells, which communicate with it (Pl. II, Fig. 8). This space is formed by the confluence of lacunæ in the early trophoblast; it is, therefore, of fœtal origin and lined by the trophoblast.

Maternal vessels come to open into the I.V.S. It is the endometrial veins that first establish communication, at the eleventh or twelfth day; only at a distinctly later date can the terminations of the coiling (spiral) arteries be found to discharge into the space. Initially, therefore, the maternal blood supply to the I.V.S. is in the nature of a venous ebb and flow. Not until the arterial connections are established can an actual circulation of maternal blood in the space occur. Furthermore, the trophoblastic villi, which differentiate in the trabeculæ of the I.V.S., do not possess a blood circulation until the embryonic heart commences to beat at about the twentieth day after fertilization. By this time, however, the embedded chorionic vesicle is approximately spherical in shape and possesses a diameter of about 7 mm. Up to this stage, therefore, and as a consequence of the absence of an embryonic circulation, no direct means exists for the transport of required metabolites to the embryo, across what are, from the sixteenth day onwards, quite considerable distances. Diffusion and, possibly, a slow circulation of the fluids in the intrachorionic, extra-embryonic spaces must be sufficient to meet the requirements of growth and differentiation. Certainly no "placental membrane" in the usual sense of this term, and which I shall be considering later, yet exists. Nevertheless, the embryo and its membranes grow and the chorionic vesicle takes up fluid and expands.

The I.V.S. during this period remains very small. As it is supplied chiefly by venous blood the hydrostatic pressure in it cannot but be very low. Two problems, therefore, are presented by the situation. Firstly, how does the trophoblast take up the required metabolites? And, secondly, how, in fact, are these substances transferred to the embryo?

An attempt to answer the first of these questions involves a brief consideration of the cytoplasmic surface presented to the maternal organism by the conceptus. Immediately after implantation this surface is syncytial in nature and over large areas of the maternal-fœtal boundary it will remain in this condition throughout gestation. In some regions, however, the boundary syncytium becomes differentiated into, or is replaced by, cytotrophoblast. The early syncytium is clearly destructive to maternal endometrial tissue, and the presence in it of phagocytosed red blood cells and other debris shows that it can engulf particulate matter. The question, therefore, essentially is:—How does the syncytium take up particles such as these which are large enough to be readily seen with light microscopy? Unfortunately, electron microscopy has not yet been exploited in the study of the trophoblast in very young stages of human implantation. By comparison with observations (Boyd and Hughes, 1954) on the fine structure of the chorionic villus in older human placental specimens, however, it can be suggested that the early trophoblastic cytoplasm possesses an apparatus which enables small droplets of fluid to be taken up (pinocytosis) and particles of greater than molecular size, such as red blood cells or cytoplasmic debris, to be engulfed (phagocytosis). On extensive parts of the surface of the chorionic villi of later stages and of the early syncytium lining the I.V.S. a so-called 'brush border' can constantly be seen with light microscopy. When ultra-thin sections of this brush border are examined with the electron microscope it is found to consist of myriads of microvilli which may, individually, be as much as 2 μ in length. We recorded the presence of numerous vacuoles in the syncytial cytoplasm underlying the microvilli, and suggested that, in the human placenta, the microvilli were wafting fluid into the cytoplasm. Such pinocytosis had, in fact, been suggested earlier by Wislocki and Bennett (1943) from their observations based on light microscopy. Later E.M. studies on the human placenta by Wislocki and Dempsey (1955) and by Sawasaki, *et al.* (1957), have supported such an interpretation for the brush border. By analogy the presence of the brush border in the early implantation stages leads to the conclusion that when the trophoblast of such stages comes to be investigated with the E.M. it will be found to possess microvilli such as are present on the syncytial covering of the chorionic villi of an embryo of as early as the 6 mm. C.R. length stage. I suggest, therefore, that from the earliest stages of placental development, the syncytium does not behave merely as a semi-permeable membrane. Through the possession of a brush border, constituted by the microvilli, the engulfing of substances in the form of particles even larger than the largest macro-molecules is possible.

This suggestion can be supported by other observations. In the first place there is histochemical evidence. It has already been stated that the uterine glands produce a copious secretion and that through the cytolytic activity of the

trophoblast this secretion can come into intimate relation with the syncytium. One of the products of secretion is glycogen which can be readily identified histo-chemically. In implantation sites of somite embryos (Boyd, 1957) glycogen can be identified in large amounts in the decidua, in the cells of the uterine glands, and in the glandular lumina. It is also present in the cytotrophoblast, in cytotrophoblastic spaces, in peripheral bays of the I.V.S., and in areas of the syncytial covering of the villi orientated towards the endometrium (Pl. III, Figs. 9 and 10). In this last site the glycogen can be seen at all levels between the surface, facing the I.V.S., and the deeper part of the syncytium, where it is particularly heavily concentrated. Small glycogen particles can be seen to have been caught up in the brush border and the appearances suggest strongly that they are being phagocytosed by the syncytial surface. Equivalent appearances have also been described recently by McKay, *et al.* (1958), in a report on the distribution of glycogen in the syncytium of early human implantations. Observations on the behaviour of pigment granules found in the cells of, and presumably produced by, some of the uterine glands also point to the conclusion that there is active syncytial phagocytosis. These granules can be found not only in gland cells (Pl. III, Figs. 11 and 12); they are also present in the adjacent cytotrophoblast (Pl. III, Fig. 13), in the brush border, and in the general syncytial cytoplasm of related villi (Pl. III, Fig. 14).

Observations such as these on the human placenta, and much experimental work on mammals with very different placental structure (Brambell, *et al.*, 1951); Brambell, 1959; Wislocki, 1955; Dempsey, 1958) indicate that the placenta cannot be regarded as a simple semi-permeable membrane, permitting only of passive diffusion. Active transport mechanisms are also at work. There will, of course, be differences between the transfer of macro-molecules (and, as I have suggested, even of particulate matter) on the one hand, and of electrolytes and gases on the other. But it seems most likely that for the passage of all substances across the placental barrier cytoplasmic activity is involved. According to the nature of the substances transferred, the placental type, the actual region of the placenta, and its age, this transference involves, to differing degrees, such mechanisms as enzymes, "carrier" molecules, phagocytosis and pinocytosis. Grosser, who made considerable contributions to our knowledge of human and comparative placental morphology (summarised in 1927), based his well-known and widely accepted classification of the placenta on the degree of intimacy of fusion of the fœtal and maternal tissues. His terms epithelio-chorial, syndesmo-chorial, endothelio-chorial and hæmo-chorial, arranged in this order, give a striking summary of the diminution in the width of the tissues separating the maternal and fœtal bloods in different mammalian types. As Wislocki (1954) and others have shown, however, the gradual reduction in width of the thinnest placental regions is not nearly as dramatic as Grosser's classification suggests. In my opinion it is now quite clear that deductions relating to placental transfer and to relative placental efficiency from Grosser's classification are not well founded. Indeed such deductions can be very misleading.

The suggestion that there can be an active uptake of macromolecules by the

placental membrane is supported by our knowledge on the transfer of homologous antibodies from mother to fœtus. Indeed, plasma proteins in general appear to be able to transgress the barrier (Schechtman, 1957). The amounts of such proteins transferred may only be in trace quantities and devoid of metabolic significance. But that macromolecules can get across at all is the important and impressive fact. It is, however, possible that, once transferred, and through enzymatic breakdown, they contribute smaller molecules which can be used in embryonic synthesis. If the foreign protein macromolecules, even when they are only transferred in trace amounts, are not broken down special problems arise in relation to the antibody system of the fœtus, which, as is now well known, does not become operative until relatively late in development. Moreover, it is conceivable that the addition of macromolecules of specific pattern to the orientated molecular population of the embryo could have profound morphogenetic significances (Weiss, 1950).

Apart from the transference of macromolecules in trace amounts, however, there remains the possibility that some substances are being transferred in quantities sufficient to have metabolic importance and to serve as sources of energy or of structural material for the embryo. The great significance of glycogen, in this regard, will be obvious for the advantages of the ready availability of this polysaccharide to a system which is as relatively anærobic as the early implanted ovum would appear to be needs no stressing. What happens to the glycogen when it transgresses the syncytial surface is, of course, part of the second of the two questions I asked in an earlier paragraph. Some of it, at least, is probably broken down and utilised in the syncytium itself. Some of it may pass as glucose into the embryonic fluids and thence to the embryo. There is even the possibility that, in the early stages, some of the glycogen may be transferred as such to the embryo. A fact which, I think, is of particular significance is that the availability of glycogen in large amounts is largely restricted to the early stages of human placentation. With disappearance of the basal decidua, and of the associated uterine glands, glycogen diminishes in the villi and disappears from the syncytium. When it is remembered that a free circulation in the I.V.S. is established late, so that the early conceptus is under conditions of distinct anærobiosis, the particular association of glycogen with early development is, perhaps, not surprising.

In the latter stages of development, however, it is the maternal circulation in the I.V.S. which is of paramount importance in the supply of oxygen, electrolytes, and the basic nutritive substances to the growing fœtus. Nevertheless, our knowledge of the mechanism of this circulation is still meagre. The generally accepted view in the first three decades of this century stemmed from Bumm (1893), who considered that the endometrial spiral arteries opened on the placental septa well away from the basal plate and that the uterine veins opened about the middle of the uterine surfaces on the maternal cotyledons. By this arrangement he considered that the circulation of the blood through the I.V.S. was explained. His conclusions, it should be noted, were based on the histological study of delivered placentæ. Much more recently Spanner (1935, 1936) restudied the

anatomical arrangements by the injection techniques and concluded that Bumm's explanation was unacceptable. Spanner described the endometrial arteries as opening into the I.V.S. through the basal plate itself, and not on the placental septa. Furthermore, he considered that the maternal blood, on reaching the I.V.S., was guided by the septa towards the chorionic plate, whence it was *all* drained to the periphery of the placenta. Spanner described, in this situation, the constant presence of a dilated portion of the I.V.S. which he called the "marginal sinus." In his opinion it was only at the placental margin, and by way of this sinus, that communication was established with the uterine veins. Thus he readily explained the circulation in the I.V.S. and his interpretation was widely accepted. In particular his concept of a marginal sinus has been eagerly seized upon, especially by the clinicians, for it has been considered to provide an adequate and satisfying explanation for certain hæmorrhagic catastrophes of pregnancy. A number of investigators, however, including Hamilton and Boyd (1951) have not been able to confirm all of Spanner's findings, and consequently cannot accept his interpretation of the circulation in the I.V.S. Hamilton and I have based our study on a large number of *in situ* placentæ available in extensive serial section. We have found the openings of the endometrial arteries, into the I.V.S. of the mature placenta, to be distributed at intervals over the whole of the basal plate. I, myself (1955), have, by computation, estimated that at the fourth month of gestation there are between 100 and 150 such arterial openings; at term the number varies between 180 and 320. Spanner considered that there were about 500 such arterial communications with the I.V.S. When it comes to the veins draining from the I.V.S., however, the situation is quite different from that envisaged by Spanner. Thus a marginal sinus of the I.V.S. is not constantly present (Pl. IV). Moreover, venous openings from the I.V.S. are to be found regularly, and freely, over the whole of the surface of the basal plate. This surface, of course, includes the placental edge; it is, therefore, not surprising

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PLATE I, Fig. 1. Human embryo (H.789) of 33 mm. C.R. length in its chorionic sac, to show the implantation site and general relationships of the developing placenta. (X 1.25).

Plate I, Fig. 2. Chorionic sac and developing placenta of the same specimen shown in Fig. 1 after removal of the embryo. The cut umbilical cord is attached to the chorionic plate of the placenta. The basal placental plate appears as a whitish line across the greater part of the implantation area. This line separates the chorionic villi and I.V.S. from the basal decidua. The decidua capsularis (reflexa) shows an extension of villi and I.V.S. in relation to its lower half. The upper part of the capsularis, however, together with the abembryonic portion of the chorion, is markedly attenuated. In this region, consequently, the interior of the chorionic sac is separated from the uterine lumen by only a very thin double layer of maternal and fœtal tissue. The decidua parietalis (vera) can be seen on either side of the placenta, extending up to the cut margin of the uterus. (X 1.25).

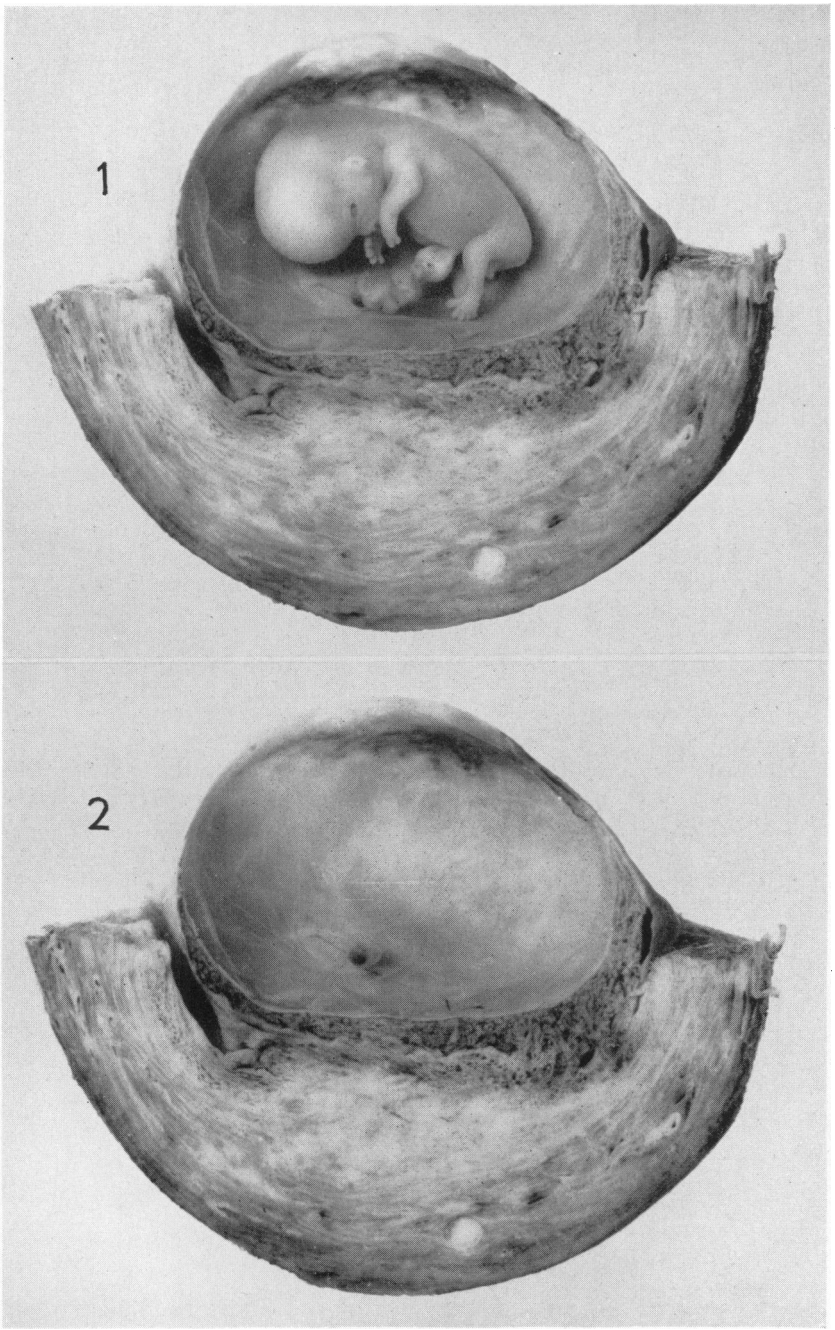

PLATE I

PLATE II, Fig. 3. Two clumps of syncytial cells in the myometrium of a uterus from a 157 mm. C.R. length human pregnancy (H.219). There is no sign of any cellular reaction to the presence of these masses of syncytium which are interpreted here as being of fœtal origin. (X 110).

Plate II, Fig. 4. High power view of one of the masses of multinucleated cytoplasm shown in Fig. 3. (X 480).

Plate II, Fig. 5. Two syncytial sprouts in a uterine vein well removed from the region of placental attachment in the 157 mm. specimen (H.219). (X 140).

Plate II, Figs. 6 and 7. Higher power views of the syncytial sprouts shown in Fig. 5. Such sprouts pass in the mother's venous blood to her lungs. They possess diameter of up to 70 microns. (X 480).

Plate II, Fig. 8. Section of portion of implantation site in a 28 somite (26-day) human embryo (H.710) to show a (V-shaped) space in the cytotrophoblast. This space contains glandular secretion and cellular debris together with a syncytial sprout. Two necrotic glands are present in the photo-micrograph. The peripheral part of the I.V.S. is shown above, surrounding the chorionic villi.

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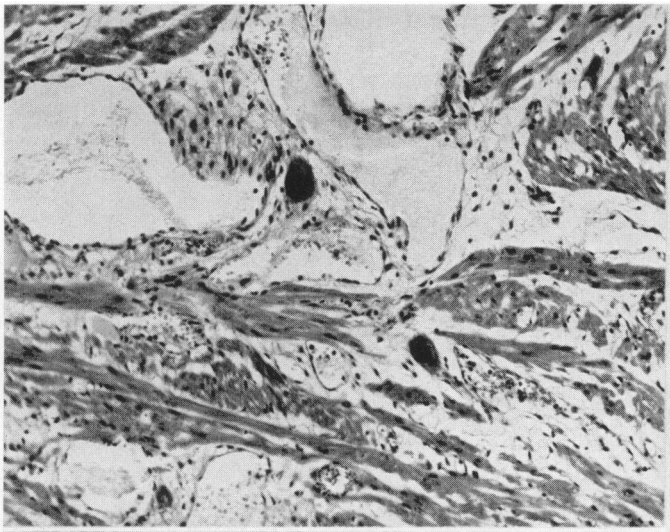

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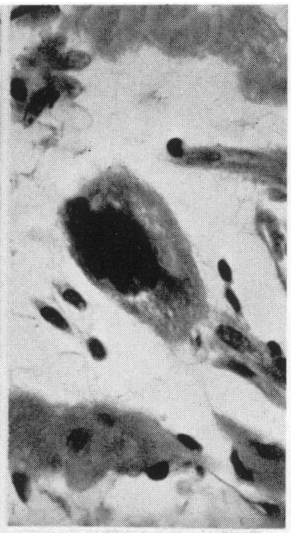

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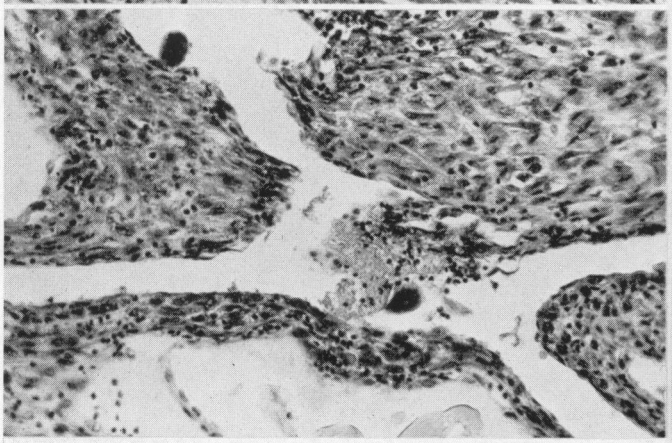

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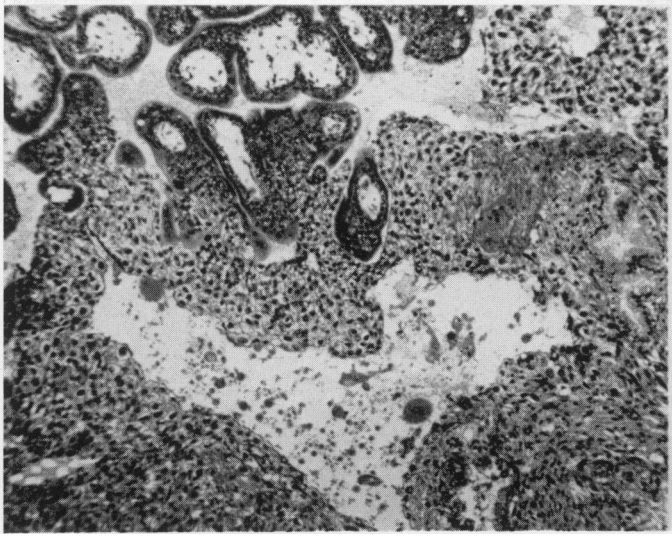

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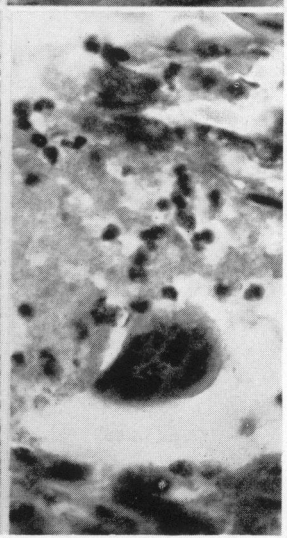


PLATE II

PLATE III, Fig. 9. Section of margin of chorionic villus from a somite human embryo to show distribution of glycogen which is darkly stained by the P.A.S. technique. Note the heavy concentration of glycogen in the syncytium which is in contact with the I.V.S. (X 535).

Plate III, Fig. 10. Section of margin of chorionic villus from a somite human embryo, stained with the P.A.S. technique. Note heavy concentration of glycogen in the syncytium on the right side of this photo-micrograph. Small glycogen particles can also be seen in the brush border bounding the I.V.S., which is situated above. (X 840).

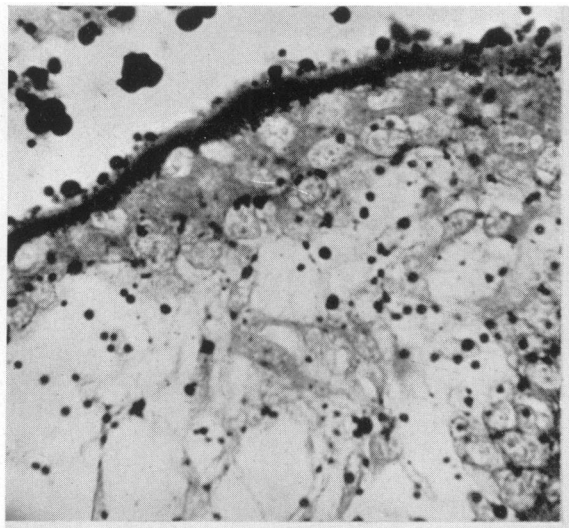
Plate III, Fig. 11. Section of basal decidual gland in a somite human implantation site to show distribution of pigment granules. (X 125).

Plate III, Fig. 12. Higher power view of part of wall of gland shown in Fig. 11. (X 610).

Plate III, Fig. 13. Pigment granules in cytotrophoblast of somite human embryo. This cytotrophoblast is situated adjacent to the gland shown in Figs. 11 and 12. (X 610).

Plate III, Fig. 14. Pigment granules in syncytiotrophoblast adjacent to the gland shown in Figs. 11 and 12. (X 610).

9.



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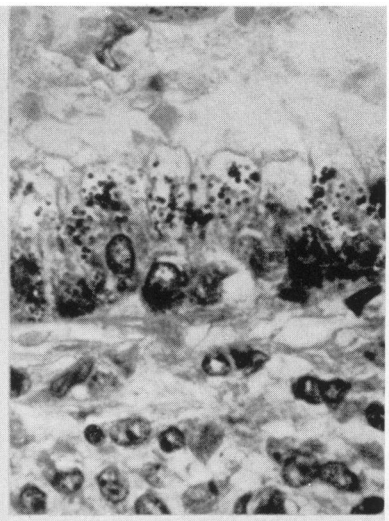

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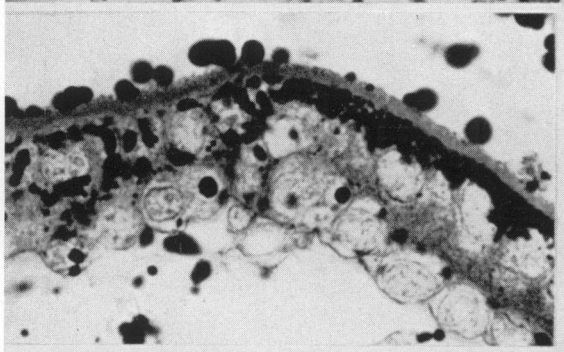

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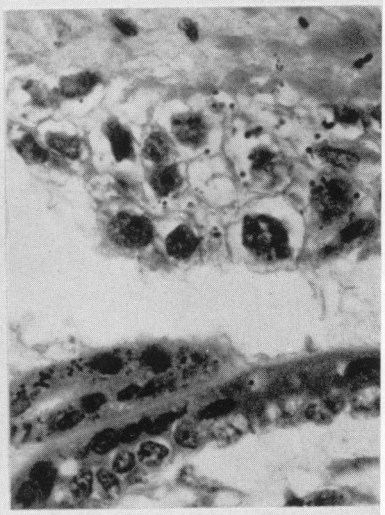

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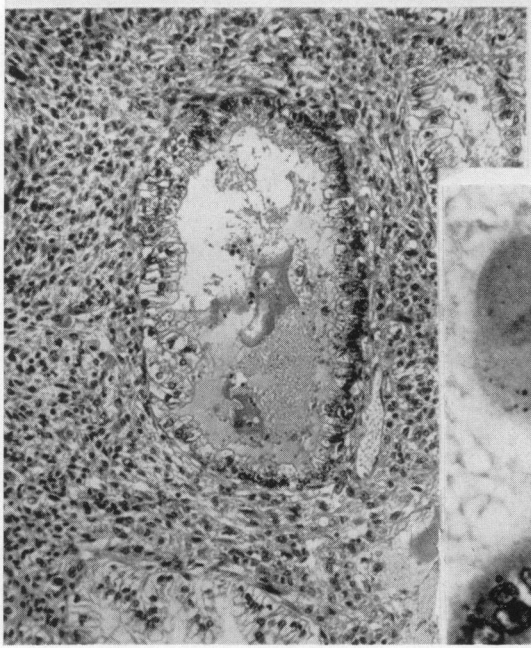

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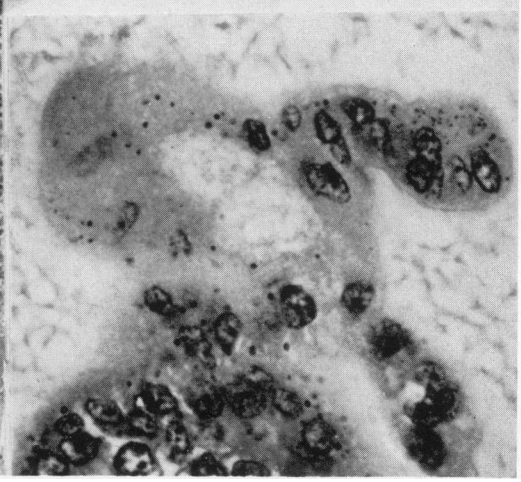

PLATE III

PLATE IV, Fig. 15. Section of an *in situ* placenta from a 260 mm. C.R. length human pregnancy. Note absence of marginal sinus and uterine venous plexus related to central part of basal plate. By this stage the whole of the uterine lumen has been obliterated and the decidua reflexa has fused with the decidua parietalis. The amnion can be seen as a fine membrane lining the whole of the chorionic cavity. The density of the villi in the I.V.S. is, in general, uniform, but there is some appearance of a sub-chorial lake in relation to the central part of the chorionic plate. (X 2.5).

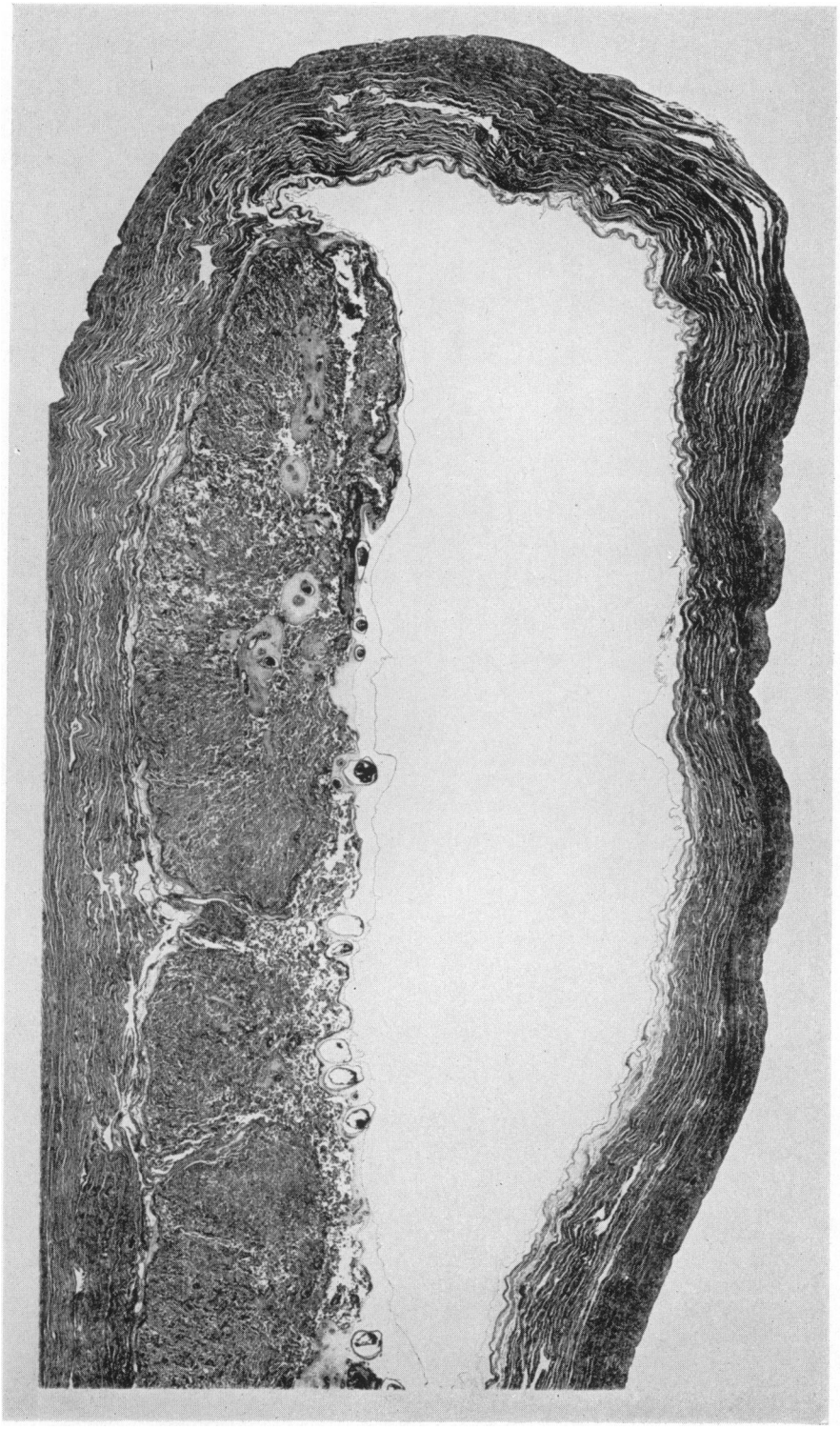

PLATE IV

that, from time to time, communications can actually be found passing from the marginal portion of the I.V.S. to the decidual veins. Hamilton and I are convinced, however, that there is free drainage of the I.V.S. into veins that communicate with it over the whole basal surface of the placenta. Finally, we follow Stieve (1942) in considering that the arrangement and nature of the placental septa is such that these curious, and ill-understood, partitions cannot serve the function allocated to them by Spanner.

The I.V.S. is, of course, an enormous and complicated arterio-venous anastomosis. With the arrangement of its afferent arteries and efferent veins, such as I have described, the problem arises as to how, in fact, the arterial blood entering the space from the spiral vessels is prevented from being short-circuited into the orifices of the contiguous veins on the basal plate. Dr. Elizabeth Ramsey (1955) has suggested, for the macaque monkey placenta, that the head of pressure in the endometrial arterial orifices is sufficient to drive the blood towards the chorion and that thus, and without the need of the septa to act as baffles, or "dividers," short-circuiting is avoided. Her suggestion has been supported by Borell's (1958) studies on the human placenta, using arterioradiographic techniques. In my opinion, however, we do not yet know sufficient about the I.V.S. itself, or about the pressure conditions in it to be able to accept with complete assurance Dr. Ramsey's interpretation. There may, for example, be preferential pathways in the I.V.S. The existence of such pathways could, indeed, explain certain features in placental infarction. The Braxton-Hick's contractions of the myometrium may also come into the explanation. Furthermore, there are extraordinary alterations in the arterial structure which, as they seem capable of influencing the pressure conditions, must be taken into account in explaining the I.V.S. circulation.

This last statement leads to a, necessarily brief, consideration of these coiling, or spiral, endometrial arteries. Discovered in the early eighteenth century and described in some detail by William Hunter in the classical account of the decidua in his *Anatomy of the Gravid Uterus*, these arteries undergo marked changes in the course of the non-pregnant uterine cycle. During pregnancy the alterations in the vessels are even more remarkable (Boyd, 1955). They are tapped by trophoblastic erosion relatively late in implantation and they then soon show several remarkable alterations. In the first place, and at an early stage of development, their walls in the near vicinity of the placenta show a striking degenerative appearance, involving hyaline necrosis and disappearance of the muscle cells in the *media* of the vessels. If a single spiral artery is followed from the myometrium to its termination in the I.V.S. one segment of it is often found to be very much narrowed before the region of terminal dilatation, near its orifice, is reached. If this narrowing and the spiral nature of the vessels are together taken into consideration it can be concluded that, in life, the blood pressure in the arteries is very much reduced along the length of their course. Finally, however, and perhaps most remarkable of all the arterial modifications, many of the spiral vessels come to contain within their lumina cells of uncertain nature. Some of these intra-arterial cells are certainly of fœtal origin, being

derived from the cytotrophoblastic shell. Some, however, may be of maternal origin, for they could be derived from the arterial endothelium or even from the decidua. Such cells, whatever their origin, are found in many of the spiral arteries, and often at quite considerable distances from the basal plate, until as late as the sixth month of gestation. None of us has any adequate notion as to their precise significance. Their presence in the vascular lumen must, however, add to the general cutting down of the blood pressure in the spiral arteries which contain them. In many vessels, indeed, these cells are so numerous, and become so crowded, that blood-flow in these arteries must be reduced to near, or even complete, cessation.

Such aggregations of cells are only found in the spiral arteries—they are never seen in the veins opening out of the I.V.S. The veins themselves are thin-walled and show none of the alterations that might be expected if arterial pressure was being transmitted to them. Not infrequently, however, other plugs, formed by the tips of adjacent chorionic villi, are found to extend into the veins. Such "herniation" of villi into the venous orifices may only be a post-mortem effect and due to contraction of the uterine muscle. Whether this is so, or not, the herniated villi can readily be identified in sections of *in situ* placentæ, a fact that is most useful in identifying the venous orifices from the I.V.S.

Finally, I come to the intervillous space itself. To deal with it adequately would require at least a whole lecture, and such an attention to anatomical and histological *minutiæ* that your attention might well not be held. In summary, however, I can say that the space is very extensive and that, both in shape and in capacity, it probably fluctuates widely during life. It is lined almost, but not quite, entirely by syncytio-trophoblast and, as has been described earlier, this syncytium shows a brush border constituted by myriads of microvilli. It is through the syncytium that the maternal-fœtal exchanges, in both directions, take place. Whether these exchanges are active, as the evidence strongly suggests, or passive, the total area of the syncytium will be one important factor in determining the amount of the transference of substances. Estimations by different investigators of the total area available for exchange, which, in effect, means the total villous surface, vary from four to fourteen square metres for the mature placenta, with the consensus of opinion inclining towards the larger estimation. Even allowing for possible errors in estimation and considerable variations from placenta to placenta, the total area for exchange is certainly a very large one. It corresponds closely, as Wilkin and Bursztein (1958) have pointed out, to the total absorptive surface area of the intestinal tract of adult man. And the area must provide a considerable safety factor in placental function. The deposition of fibrinoid and of fibrin itself in the I.V.S. commences early in development and by the time of placental maturity is often very extensive indeed. The presence of these deposits on the villi must cut down considerably the efficiency of the syncytial membrane. Often, also, there is extensive formation of thrombi in the placenta. I have seen late placentæ in which anything from one-third to one-half of their substance must have been rendered functionally ineffective by such quasi-pathological changes. And yet these placentæ had been

efficient enough to provide adequately for the growth and differentiation of their dependent fœtuses, for these were of size and weight proportionate to their developmental ages. The existence of this very high margin of "placental reserve" is not the least of the many puzzling features of the maternal-fœtal relationship. Like the length of so many umbilical cords, the functional capacity of the placenta is, in relation to the exchange problem, much in excess of what is normally required of it. This excess may be due to some, possibly temporary, wide mesh in the sieve of natural selection. It may, however, have some quite different explanation. Thus the placental tissues produce important hormones, and the final size of the organ may be related to this aspect of its function rather than to the part it plays in the two-way traffic in metabolites.

In the time at my disposal I have only been able to draw attention to a few facets on the rough unhewn rock that constitutes the unopened core of the placental problem. The organ has not received anything like the attention its importance demands, and will, I feel sure, increasingly receive. It did not even receive a name until 1558 when Realdo Columbus, in his *De re anatomica*, first used the term placenta. Four hundred years, you may think, is not a short time in the history of science. In fact, however, it has effectively been only the last hundred years that has given us our present-day knowledge of the placenta. And the number of those who have worked on it is so small that I could readily list most of them for you. We can look forward, I believe, to a continuing expansion of interest in placental morphology and function.

And, surely, the placenta will deserve this increasing attention, for it is the essential structural basis of the prenatal relationship between mother and child. Devoid of a direct nerve supply, it integrates itself into the *milieu intèrne* of two organisms. Derived by differentiation from cells that possess the potentiality of living for seventy, or more, years, its constituents sacrifice themselves after ten lunar months. Built up of disparate cytological elements derived from two heterozygous individuals, it has functions so diverse as to overlap those carried out, in the adult, by lungs, liver, intestinal tract, kidneys, and endocrine glands. Wordsworth certainly did not have the placenta in mind when he wrote:—

> "there is a dark
> Inscrutable workmanship that reconciles
> Discordant elements, makes them cling together
> In one society."

Nevertheless, the quotation, in the present context, is apt. For any satisfying explanation of the relation of the unborn child to its mother the darkness of the intra-uterine workmanship must first be made visible and the inscrutability replaced by biological answers to rational questions. In the course of satisfying our curiosity on the placenta there can, in my opinion, be no doubt that obstetrics and pediatrics will be forwarded. It is because I strongly hold this opinion that I have dared to present a non-clinical subject in an oration that has as its prime purpose the perpetuation of the memory of a distinguished clinician.

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NEUROSURGICAL TREATMENT OF PARKINSONISM AND ALLIED DISORDERS OF INVOLUNTARY MOVEMENT (DYSKINESIÆ)

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ADDRESS

given to the Ulster Neuro-psychiatric Society on 21st November, 1958

SURGICAL attempts to relieve disorders of involuntary movement (dyskinesiæ) date from the excisions of cerebral cortex first practised in 1890 by Sir Victor Horsley. His three patients, suffering from choreoathetosis, had gratifying results which, however, were not easily reproduced by other surgeons of the period. The development of ancillary neurological investigative methods later permitted more accurate excision of motor and premotor areas of the cerebral cortex with relief of Parkinsonian tremor and choreoathetotic movements (Bucy and Case, 1939), but at the expense of contralateral hemiparesis and usually without relief of rigidity. Operations on the internal capsule, cerebral peduncle and spinal cord have the same drawback and none have gained wide acceptance. Recently operations have been evolved in which lesions are produced in certain parts of the basal ganglia or their efferent fibres. Abolition or relief of involuntary movements, tremor, and rigidity has been obtained without coincident hemiparesis. Such operations are now in routine use in a few clinics in Europe and North America. Their development must be considered relative to the anatomy, physiology, and patho-physiology of the subcortical nuclei making up the basal ganglia.

To the anatomist the basal ganglia comprise the caudate nucleus, putamen, globus pallidus, and amygdaloid nucleus. The caudate and putamen, having identical histology and close anatomical connections, are sometimes considered a single organ and are together named the striatum because of their striated appearance on section. The globus pallidus and the putamen are described together on naked eye structure as the lentiform nucleus, but it should be emphasized that the globus pallidus has a very different microscopic structure and is more closely allied to the subthalamus. Neurophysiologists, as a result of recent work, have added to the anatomical classification several other important structures to form a functional group. These additions are the subthalamic nucleus (corpus Luysii), the red nucleus and substantia nigra in the upper mid brain, and certain cerebellar connections, notably the dentate nucleus and brachium conjunctivum. What we are dealing with, then, is that group of structures concerned with motor function exclusive of the conventional pyramidal system.

The fibre connections of the basal ganglia are very complex, the pallidum in particular being at the cross-roads of multiple ascending and descending tracts coming from cerebral cortex, striatum, thalamus, cerebellum, subthalamus and hypothalamus. The efferent group leaving the posterior margin and the medial tip of the globus pallidus in the ansa lenticularis is especially important. It reaches the ventrolateral nucleus of the thalamus by way of the fields of Forel, forming a linkage which is the principle surgical target in the treatment of Parkinsonism. The network of interconnecting fibres between the subcortical nuclei represents, in all probability, examples of closed circuit arrangements linked up into what, under normal conditions of health, would be a balanced self-regulating mechanism along the lines of an analogue computor. By way of illustration, the simplest circuit in the body is probably the arc from anterior horn cell to muscle spindle to posterior horn cell and, by one or more internuncial neurones, back to anterior horn cell. Information from this arc and the influence on it of other systems constitutes the neural mechanism for maintenance of body posture. A current view is that interruption of the neurological balance of such circuits in the brain disturbs dynamic equilibrium and the various dyskinesiæ result.

The physiology and pathophysiology of the basal ganglia may be considered under the usual headings for the neurophysiological investigation of the nervous system:

(i) the effects of electrical stimulation,

(ii) the effects following lesions or extirpations,

(iii) the study of naturally occurring disease.

(1) In the past fifteen years many studies have been made of the electrical properties of the basal ganglia and reticular formation. Animals with permanent depth electrodes in position are used in such experiments. A 60 c/s current up to 20 v. applied to the globus pallidus causes no movement of the contralateral musculature while a stimulating current of 2 v. in the internal capsule causes marked contractions of the contralateral limb musculature. Direct stimulation of the striatum, red nucleus, subthalamic nucleus and substantia nigra produces only increased tone of the axial musculature and does not cause tremor or movements of the limbs. Generally speaking, cortical stimulation evokes no response in the basal ganglia.

(2) Direct experimental lesions in the extrapyramidal system have, with two exceptions (subthalamic nucleus and brachium conjunctivum), produced few or no neurological deficits. Even large caudate and lenticular lesions are usually without effect. Athetoid movements have occasionally followed putamen lesions but have never followed globus pallidus lesions. Lesions placed in the subthalamic nucleus are usually accompanied by varying degrees of choreoathetosis or even by hemiballismus. A few cases of surgically induced lesions in humans have resulted in the same condition; it has also followed head injuries and vascular lesions. The other structure, lesions of which cause disorder of movement, is the dentate

nucleus of the cerebellum or its efferent fibres in the brachium conjunctivum. Lesions here produce action and static tremor accompanied by ataxia, if they are sited below the red nucleus.

A recent extension of this approach has been made by Carpenter (1958), who, after producing abnormal movements by the methods just mentioned, proceeded to make further lesions in various other parts of the nervous system in an attempt to abolish the induced movements. It was soon apparent that interruption of corticospinal fibres at their cortical origin or along their course would decrease or abolish movements but only at the expense of hemiparesis. Recovery of hemiparesis usually was accompanied by reappearance of the movements. Apart from this fibre tract, the only other lesions which affected tremors were those in the globus pallidus, where a 10 per cent. by volume lesion was successful, especially if placed medially in the nucleus. Here we see the experimentalist using methods similar to those which will be mentioned shortly as having proved effective in the relief of symptoms of Parkinsonism and other movement disorders in humans. And here also we see the basic concept of such operations; namely, that they aim, as it were, at correcting a neurological imbalance by producing a further lesion in a structure which itself is not necessarily the seat of any pathology. Clearly they are not curative procedures in the sense of removal of a diseased part or correcting directly a malfunctioning organ. What we shall be interested in is the sort of compromise which can be effected by surgery.

(3) The third contribution to knowledge of the pathophysiology of the basal ganglia is the study of diseases in man termed dyskinesiæ. The relevant disorders are paralysis agitans, post-encephalitic Parkinsonism, dystonia musculorum deformans, double athetosis, Huntington's chorea, and the neurological sequelæ of Kernicterus. It would take too much space to examine the diseases one by one. But the outstanding feature of clinico-pathological correlation, and the chief obstacle to interpretation, is the discrepancy between the lesions found and the symptomatology. Thus, in some of the worst cases of dystonia musculorum deformans, hardly any gross lesions are found. On the other hand, widespread destruction of the basal ganglia may be present without any clinical accompaniment. With such imperfect knowledge of the physiology of the region it is quite impossible to decide whether a functional disturbance is related to an observed structural change. In other words, the fact that this or that nucleus is involved on pathological examination is no foundation for saying that destruction of the nucleus is the cause of the particular clinical syndrome. An analogy of this point might be drawn from another syndrome—Wernicke's encephalopathy. Here, in a fully developed clinical case with paralysis of ocular movements and nystagmus, the only demonstrable lesion may be hæmorrhage in the mamillary bodies of the hypothalamus. This does not mean that the mamillary bodies control eye movements, yet one still finds examples of the same kind of reasoning in statements that tremor and rigidity in Parkinsonism are attributable to lesions of the globus pallidus and striatum. Actually Greenfield (1953) pointed out that the structures most heavily involved in Parkinsonism are the substantia nigra, the locus cæruleus, and the dorsal nucleus of the vagus. When a series of cases is examined it appears

that lesions in only two sites have fairly common clinical accompaniments and these compare closely with recent experimental work already mentioned. Lesions in the subthalamic nucleus often are associated with contralateral choreathetosis or hemiballisumus (Purdon Martin, 1927) and static tremor occurs with lesions in the tegmentum, presumably those affecting the dentate nucleus efferents. The notion of lesions affecting specific structures in Parkinsonism may therefore have to be changed. Bucy postulates multiple circuits serving as long and short connections between various parts of the brain and suggests that interruptions of a circuit may allow uninhibited action of certain structures. The clinical picture may, for example, represent a release of function of the globus pallidus, in which case surgical ablation could be regarded as a means of redressing the neurological balance.

To summarize this section on the pathophysiology of the basal ganglia, it may be inferred from study of human subjects and from the work of Carpenter on the effects of pallidal lesions in the monkey, that the integrity of the globus pallidus and its efferents to the ventrolateral region of the thalamus is essential in the production of the dyskinesiæ. Surgical lesions of the globus pallidus might, therefore, be expected to diminish the abnormal movements. A tentative explanation may now be offered as to why these various abnormal movements respond only to destructive lesions of globus pallidus, motor cortex or corticospinal fibres. It is possible that the vital pallidofugal fibres pass to the thalamus and are relayed from there to the cortex to join the corticospinal bundles and that it is only by this circuitous route that pallidal impulses reach segmental levels. In short, the corticospinal tract conveys impulses from both cortical and subcortical levels.

Surgical Advances in the Dyskinesiæ

Following Horsley's early operations only sporadic reports appeared for the next thirty years. Klemme (1940) applied the improved techniques of cortical excision to Parkinsonian patients but stressed that hemiparesis would result. Putnam (1938) introduced dorsolateral cordotomy, a method which has been elaborated by Oliver (1953). Section of corticospinal fibres in the internal capsule (capsulotomy) was advocated by Browder (1948), and Walker (1952) suggested section of fibres in the cerebral peduncles (pedunculotomy). In all these operations hemiparesis is usually the price which must be paid for relief of tremor. Parkinson himself noticed that when a patient with paralysis agitans had a stroke with hemiplegia, tremor was abolished.

Meyers (1941) was the first to study the effects of lesions remote from the conventional pyramidal tract. After a series of open operations on the caudate nucleus, putamen and globus pallidus he found that the most effective lesion was one in the efferent fibres at the medial margin of the globus pallidus (the ansa lenticularis). Unfortunately the mortality of these extensive operations was over 12 per cent. Fenelon (1950) and Guiot and Brion (1953), working in Paris, devised a direct subfrontal approach to the globus pallidus which has given good results. But, again, the operation is extensive and probably carries a higher

morbidity than the stereotactic methods to be described. In 1951 Spiegel and Wycis showed that an electrode could be introduced with great accuracy through a burrhole into structures in the basal ganglia. They used a stereotactic apparatus, modelled along the lines of the experimental device introduced by Horsley and Clarke (1908). Discreet electrolytic or chemical lesions could now be made in chosen nuclei and these authors have set the pattern for current basal ganglion surgery.

The only other surgical technique which requires mention is ligation of the anterior choroidal artery (Cooper, 1954). This vessel usually supplies the globus pallidus and a variable area of the rest of the basal ganglia. Many good results have been obtained and its use will be mentioned later. It may be stressed again at this point that the surgical lesions are, in all probability, being made in a normally functioning nucleus, that is to say, we are not adding destruction to an already damaged area.

Current stereotactic techniques have in common the identification of parts of the third ventricle on an encephalogram as an initial point of reference to act as guide to the site of the globus pallidus or thalamus. The selection of this "internal landmark" is essential in the human; co-ordinates derived from points on the skull ("external landmarks") are satisfactory in some species which do not exhibit the same variations as the human. The technique of alcohol injection of the globus pallidus (chemopallidectomy) is briefly as follows:

An air encephalogram is performed and the third ventricle and foramen of Munro identified. A cannula with a small balloon at the tip (Bravo and Cooper, 1957) is then placed under radiographic control in the region to be attacked. The most successful site at which to make globus pallidus lesions is 14-18 mm. from the mid-line, 5 mm. behind and 5 mm. below the postero-inferior margin of the foramen of Munro. The balloon is now inflated with myodil (X-ray opaque) to compress surrounding tissue, the function of which is temporarily suspended. If the needle tip is by mistake, in the internal capsule hemiparesis will at once result when the balloon is inflated but this will rapidly disappear when the balloon is deflated. When the needle is sited correctly in the globus pallidus or ventrolateral region of the thalamus, however, inflation of the balloon as a rule leads to instant cessation of tremor and rigidity. The balloon is left *in situ* for 24-48 hours, after which it is deflated. A small cavity is left. Subsequently absolute alcohol is injected into the cavity to produce a permanent lesion. Originally all lesions made at such operations were sited in the pallidum; lately it has been found that lesions in the thalamus are even more effective when tremor predominates. In either case lesions are made within a few millimetres of the internal capsule, the optic tract, and the hypothalamus. One of the obstacles to accurate placement of lesions—the variations in humans from brain to brain—has now been largely overcome by the introduction of this physiological balloon test with its reversible lesion.

While this relatively simple technique of chemopallidectomy produces good results in certain types of patients, it is by no means generally applicable to all cases of Parkinsonism. It is not suitable for those with advanced disease. More

complicated methods designed to produce discreet lesions by electrolytic or cauterizing currents may be used in such patients. Although improvement will be less striking, a valuable rehabilitation will often be effected. Gillingham (1958) has elaborated the stereotactic method of Guiot. Using an image-intensifier X-ray apparatus, an electrode can be introduced with great accuracy into the basal ganglia. Preliminary stimulation is essential; if the needle is in the internal capsule movements of the contralateral limbs will occur. An advantage of this technique is that the electrode enters from the parietal region and traverses the thalamus to reach the globus pallidus. Lesions in either or both structures can be made on a single insertion.

Selection of Patients for Surgery.

This section commences with the reminder that surgery cannot be said to "cure" Parkinsonism or the allied dyskinesiæ; the most that can be said is that certain symptoms—rigidity, tremor, and other abnormal movements—can be alleviated. Some patients have as their chief complaint, however, head tremor, hypersalivation, pseudobulbar palsy, mental impairment, gait disturbance, pyramidal signs, severe weakness (akinesia), and the response to surgery of these symptoms will be most disappointing. The same may be said of associated psychiatric disorders, with the exception of reactive depression.

Patients most suited to surgery are those with tremor and rigidity wholly or chiefly unilateral and who, by reason of incapacity for work, or from embarrassment, are anxious to have treatment. Such patients comprise about 10 per cent. of the total Parkinsonian population. A further 20-30 per cent. of patients with longer standing disorder, usually bilateral, but with normal mental function and minimal other neurological signs, may also be considered for surgery. The rest, over 50 per cent. of Parkinsonian patients, have bilateral advanced disease, other neurological disabilities or mental deterioration. For this group chemopallidectomy has little to offer, but some younger patients may be considered for ligation of the anterior choroidal artery. Although the mortality is higher, very debilitated patients will sometimes respond. But it is in this group with advanced Parkinsonism that the smaller lesions placed by the more elaborate stereotactic methods have been made with relative safety (Gillingham).

Before operations are carried out full assessment of the patients is essential. Tests designed to evaluate their muscular power and co-ordination and the degree of tremor and rigidity are carried out together with psychological assessment of their reaction to stress, the level of activity relative to their disablement, and their adjustment to the condition. The results of this examination form a baseline for future comparison. A peculiar feature of patients with Parkinsonism, namely, the variability of their performance under the influence of emotion or suggestion, must constantly be borne in mind; some patients may be free of symptoms for nearly an hour after waking in the morning, others after a sudden shock, may be free for a whole day. This essential reversibility of all the features of tremor and rigidity at once poses a problem of assessment; it also supports the belief that successful treatment is possible.

Complications of Surgery.

The surgical mortality from chemopallidectomy is 2-3 per cent. Hæmorrhage is the most usual cause of death but occasionally death results from prolonged coma or pseudobulbar palsy. A small incidence of hemiplegia (2-3 per cent.) is reported, occurring usually the day after operation and being probably of vascular origin. Transient monopareses leaving no sequelæ are not uncommon. In patients with previous mental deterioration confusional states lasting some months have been described. Drowsiness of a few days' duration in mentally normal patients is sometimes seen. Other less common complications such as dysarthria, hyperthermia or hyperhidrosis usually respond to conservative measures.

Results of Surgery.

Several series of patients with Parkinsonism have now been reported (Spiegel and Wycis, 1958; Cooper, 1958).

Significant relief or abolition of tremor has been obtained in about 70 per cent. of patients and relief of rigidity in nearly 80 per cent. A relapse rate of about 10 per cent. in the two months following surgery is reported. Thereafter most of the patients remain improved. A second operation in the relapsed cases is often successful. The rehabilitation rate in persons over 65 years is low and relatively few in this age group are suitable for surgical treatment. The longest follow-up of results of stereotactic surgery is only 5-6 years, so it is still rather early to assess the final outcome.

In dystonia musculorum deformans promising results have been obtained. Cooper (1958) reports twenty-five patients operated on in the past three years. There were two deaths, two-thirds of the patients were improved; some who were bedridden are now ambulant and attend school.

Summary.

Recent work both in clinical and neurophysiological fields offer encouragement to surgical treatment of the dyskinesiæ. In Parkinson's disease about 80 per cent. of patients may be considered for operation, and current reports indicate that 60-70 per cent. should benefit significantly. It is stressed, however, that with this essentially progressive disease it is premature yet to speak of surgical cure. But the results presented in the past year indicate that worthwhile improvement is obtained; there have been few relapses following surgery for periods up to six years.

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DENTAL TREATMENT IN HÆMOPHILIA

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EXCESSIVE bleeding following minor trauma is the heritage of the hæmophilic, consequently extraction of a tooth presents a formidable problem. During the recent survey of hæmophilia carried out in Northern Ireland many of the patients had severe dental caries or septic roots resulting from simple neglect of elementary dental hygiene. The hæmophilic is usually reluctant to have dental treatment and can only be persuaded to visit a dentist when suffering from severe toothache. It is not perhaps fully appreciated by both hæmophilics and doctors that conservative dental measures such as fillings and scalings may be carried out with safety. Also in the hæmophilic the natural exfoliation of deciduous teeth is not associated with hæmorrhage of any severity. Furthermore, the presence of infection in relationship to a permanent tooth may result in such a fibrotic reaction that should the tooth subsequently exfoliate or require to be removed the area of hæmorrhage is considerably reduced.

A scheme for dental inspection and treatment has been inaugurated at this centre, in an attempt to educate hæmophilic patients in the principles of dental hygiene, and so to delay extraction for as long as possible. If it is considered essential to have dental extractions carried out, the patient is admitted to hospital, where he can be kept under observation and where serious bleeding can be dealt with without delay. For this operation the patient then becomes the responsibility of both the doctor and the dentist, working as a team.

The decision to extract teeth in a hæmophilic should only be taken when the fullest conservative measures have failed. Also the indications for extractions must be carefully considered and the danger of extraction weighed against the retention of the septic roots which may exfoliate naturally. In this centre, during the past three years, thirty-six teeth have been extracted from a total of eleven patients suffering from classical hæmophilia. Four of these patients were severely affected, four were moderately affected, and three had only mild symptoms of the disease. The hæmophilic was admitted to hospital on the day prior to extraction and a definite plan was followed. The more important aspects of this will now be discussed.

TRANSFUSION OF PLASMA AND BLOOD.

The hæmophilic patient has impaired blood clotting because of a deficiency of antihæmophilic factor in his plasma. The antihæmophilic levels in our patients varied from 1 per cent. to 30 per cent. before transfusion. It is considered that bleeding is unlikely to occur if the level of antihæmophilic is maintained consistently above 10 per cent. In an attempt to raise the antihæmophilic factor to this hæmostatic level, our patients were transfused with fresh plasma just prior to operation. The volume of plasma required to raise the antihæmophilic factor

level from 1 per cent. to approximately 10 per cent. is of the order of 1 litre and this was given an hour before operation. The importance of reaching a hæmostatic level quickly is well realised, and therefore this transfusion has to be given rapidly, i.e., in half to three-quarters of an hour. Because of the short half-life of anti-hæmophilic factor when transfused into the circulation of a hæmophilic, it is necessary to transfuse further litre amounts of plasma at twenty-four and forty-eight hours after operation. After forty-eight hours plasma was only transfused if severe bleeding occurred which failed to stop with local hæmostatic measures. Once oozing became persistent from the tooth socket it was considered important not to delay plasma transfusion, as continued hæmorrhage tends to retard healing processes and causes tissue necrosis which further depletes the level of the anti-hæmophilic factor in the circulation. Replacement transfusion with fresh whole blood was used when hæmorrhage was excessive or the hæmoglobin level had fallen.

Number of Teeth to be Extracted at One Operation.

It is wrong to assume that replacement therapy with plasma can prevent bleeding from ten or more extraction sites equally as well as from one extraction. Therefore only two or three teeth should be extracted at the one operation in moderate or mild hæmophilic cases and one tooth only in the severe hæmophilic. In most of our cases the teeth removed were in adjoining sites, which simplified the protection and treatment of the sockets.

Local Measures for Arrest of Hæmorrhage.

Three methods are available for the arrest of hæmorrhage from a tooth socket in a hæmophilic. These are (1) the use of a protective splint, (2) packing the socket, and (3) suturing the socket. These were used separately and in combination. However, it must be realised that once bleeding becomes persistent, local measures play a secondary rôle to plasma therapy.

1. *Protection*: When the patient possessed some whole teeth it was possible to construct a protective acrylic splint to cover the socket. This splint, apart from acting as a passive barrier to the hæmorrhage, protected the highly friable clot from damage or from movement caused by the normal oral functions. A certain amount of leakage occurred around the periphery of the splint, which served to relieve pressure and avoided directing the hæmorrhage into the tissues. The splint was designed only to cover the teeth in order to avoid mucosal damage in the buccal and labial regions. The splints used in the present series were all acrylic but experiments are proceeding with polyvinyl chloride attachments to acrylic splints and also to soft rubber splints. It is felt that these materials will be more adaptable to œdematous changes in the tissues. The fixation of the splint may rely on friction alone or be aided by a cement. Both methods were used in the present series. In several of our cases the splints seemed to stimulate bleeding, and the cause appeared to be due to either faulty design or faulty fit. Our experience has, however, convinced us of the value of a well-fitting efficient splint. If a splint has to be removed because it is inefficient, then it should be either discarded or adjusted to make a more accurate fit. Before any splint is reinserted, the clot

should be trimmed with scissors and the area cleansed gently with a saline swab so as to avoid disturbing as far as possible any clot over areas which have begun to heal.

2. *Packing*: This is only of limited value in the hæmophilic. The obliteration of the dead-space of the socket with non-absorbable material may temporarily cause a cessation of bleeding by pressure on the vessels of the socket. However, as the socket walls are conical, the clot tends to dislodge the pack orally. Further, if the pack does remain, it has to be removed at some point and the friction caused by the movement may precipitate further delayed hæmorrhage. However, hot saline packs have been found by the authors to be of some value during the immediate post-operative period, as the heat stimulated contraction and retraction of the vessels.

The obliteration of the 'dead-space' of the socket with absorbable material has the value of not having to be removed, but unfortunately it is often spontaneously dislodged by the blood flow. There is some danger of infection with an absorbable pack, but this is small when an antibiotic cover is used.

With both absorbable and non-absorbable materials the use of hæmostatic agents such as thrombin is of extremely limited value, as the clot formed by this substance is quickly dislodged by further bleeding. Orr and Douglas (1957) advocate Calgitex or fibrin foam soaked in thrombin as a suitable absorbable pack. The authors have used, on several occasions, an absorbable gelatin sponge soaked in thrombin.

3. *Suturing*: The value of sutures alone, or as an adjunct to packs or splints, is small and is outweighed by the damage they may do. The additional punctures provide further possible bleeding points from which severe bleeding may be induced, when the area is disturbed by the removal of the sutures. The use of sutures tends to confine the hæmorrhage within the tissues so producing a hæmatoma which may strip fresh areas of periosteum away from the bone and extend deeply and dangerously into the neck.

If the sutures are inserted with tension as advocated by Mead (1946) then pressure necrosis is likely to occur with an unpleasant secondary hæmorrhage involving the palatal or buccal mucosa where local measures may be difficult to control. When a suture was considered necessary in our cases due to laceration of the mucosa during extraction, then treble O quick absorption cat-gut was used with a minimum of tension.

Anæsthesia.

The anæsthesia used for dental extraction may be either local or general. In either method premedication is to be advocated combined, if necessary, with post-operative sedation. The majority of our cases were operated on under gas and oxygen intratracheal anæsthesia. No bleeding into the upper respiratory tract occurred as a result of using this method.

Local anæsthesia would appear to have greater attendant dangers than general anæsthesia. Archer (1952) has recorded a fatal case occurring within forty-eight hours from asphyxia due to a cervical hæmatoma after two inferior alveolar

injections of local anæsthetic for cavity preparation. Orr and Douglas (1957), on the other hand, found local infiltration in ten cases quite satisfactory but that regional inferior dental block carried the risk of hæmatoma formation. The risk of a perineural hæmatoma with resulting peripheral nerve damage must also be considered.

Control of Infection.

Secondary hæmorrhage from a tooth socket may be precipitated by infection and therefore dental extraction should never be carried out where gross sepsis is present. Under such circumstances extraction should be deferred until infection is controlled. In general we employed antibiotic cover by oral rather than by intramuscular route because of the danger of hæmatoma formation at the injection

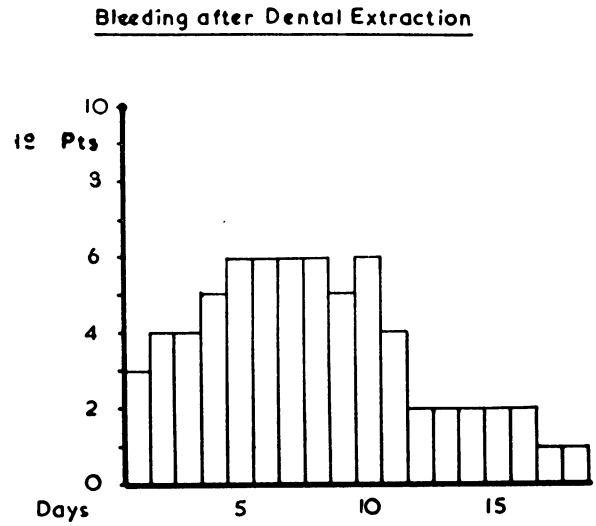

Fig. 1—Histogram illustrating bleeding following dental extraction in hæmophilics.

site. For this purpose oral penicillin in the form of phenoxymethyl penicillin was given routinely in standard dosage to every case as a pre-operative measure on the day before operation and was continued for five days thereafter. We consider mouth-washes to be contraindicated, as the active movements tend to disturb the clot and thus precipitate further hæmorrhage. Instead of mouth-washes we have used peppermint and chlorophyll tablets to overcome the foul taste caused by bleeding into the oral cavity.

Post-operative Course.

During the first forty-eight hours after extraction little bleeding occurred, and this may be attributed to the fresh plasma given in the pre- and immediate post-operative periods. In Fig. 1 the incidence of hæmorrhage occurring in the

hæmophilic patients is correlated with the number of days after operation. Oozing occurred in a few cases in the immediate post-operative period. This was generally related to the use of an ill-fitting splint. Bleeding was most marked between the fifth and the tenth post-operative day. The duration and severity of the hæmorrhage was related to the severity of the A.H.F. defect and in our experience was not correlated with the presence of a circulating anticoagulant of the Bridge type. The tendency to bleed was less marked after the tenth day. These findings are similar to those of Orr and Douglas, 1957.

Plasma and whole blood transfusions were given after the first forty-eight hours when persistent hæmorrhage occurred. In Fig. 2 a typical post-operative course in a severe hæmophilic is shown and the treatment required to cover each bleeding episode is indicated.

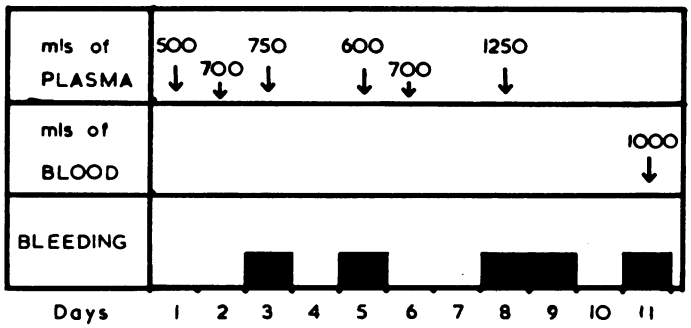

Fig. 2—Post-operative course following extraction of two teeth in a severe hæmophilic.

The period of hospitalisation varied from three days in a mild case to twenty days in a severely affected hæmophilic. The average stay in hospital was thirteen days.

When the hæmorrhage following tooth extraction was sufficient to cause a considerable iron depletion, oral iron was given after discharge from hospital until the hæmoglobin reached a normal level.

Summary.

In hæmophilia dental care is essential. Many conservative dental measures can be carried out in hæmophilics without risk of bleeding. In the management of hæmophilia an organised service providing regular dental inspection and conservative treatment is necessary. Such a service has been provided for all hæmophilics on our register in Northern Ireland.

Dental extraction should only be performed for clear indications. It always carries a considerable risk. This is minimised if extractions are carried out at a hospital where the staff has experience in the care of hæmophilics. It requires close medical and dental co-operative management.

The following are the guiding principles which underline any attempt to carry out dental extraction in hæmophilia:

1. Maintenance of a hæmostatic level of antihæmophilic factor in the circulation over the danger period.
2. The use of an efficient and well-fitting splint as a protection for the socket.
3. The application of minimum pressure on the socket or on the surrounding tissues so as to avoid ulceration and secondary hæmorrhage.
4. Minimum movement of surrounding tissues and of the clot, so as to allow organisation.
5. The prevention of infection to avoid breakdown of the clot.

Acknowledgments.

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REPORT OF THE VIRUS REFERENCE LABORATORY, QUEEN'S UNIVERSITY, BELFAST, 1958

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With J. J. McAlister, A.I.M.L.T., L. Corkin, Moya Briggs, B.Sc., and R. Nelson

THIS is the second report of the Virus Reference Laboratory established in the Department of Microbiology of the Queen's University of Belfast by the Northern Ireland Hospitals Authority. The first report covering the period 1955 to 1957 appeared in an earlier number of this Journal (Murray, Dane & Dick, 1958).

POLIOMYELITIS, ASEPTIC MENINGITIS, AND ENCEPHALITIS.

Poliomyelitis.

As in previous years, our aim has been to receive specimens from all notified cases. There were fifty-five of these in 1958, which excludes five cases originally notified but in which the diagnosis was subsequently revised. Of the clinically

TABLE 1.

SHOWING VIRUSES RECOVERED FROM NOTIFIED CASES OF POLIOMYELITIS.

NOTIFIED	No.	SPECIMENS FROM	No. FROM WHOM POLIOVIRUS Type 1	Type 2	Type 3	No. FROM WHOM ECHO OR COXSACKIE VIRUS	No VIRUS ISOLATED
Paralysed	47	45	17	0	20	0	8
Not Paralysed	8	8	2	0	2	0	4

confirmed notified cases forty-seven were paralysed and eight were not paralysed. The poliovirus types recovered from these cases are shown in Table 1.

Although serological surveys have shown that all three types of poliovirus are about equally common in Northern Ireland, this is the first year since 1955 (when isolation and typing of virus was started) that type 3 virus has been isolated from paralytic cases.

Specimens were obtained from most of these cases within a few days of onset of symptoms. The period of the year of isolation of the viruses is shown in Fig. 1 and the geographical distribution in Fig. 2. Included in these figures are five additional isolations from some additional infections and contacts which are discussed below.

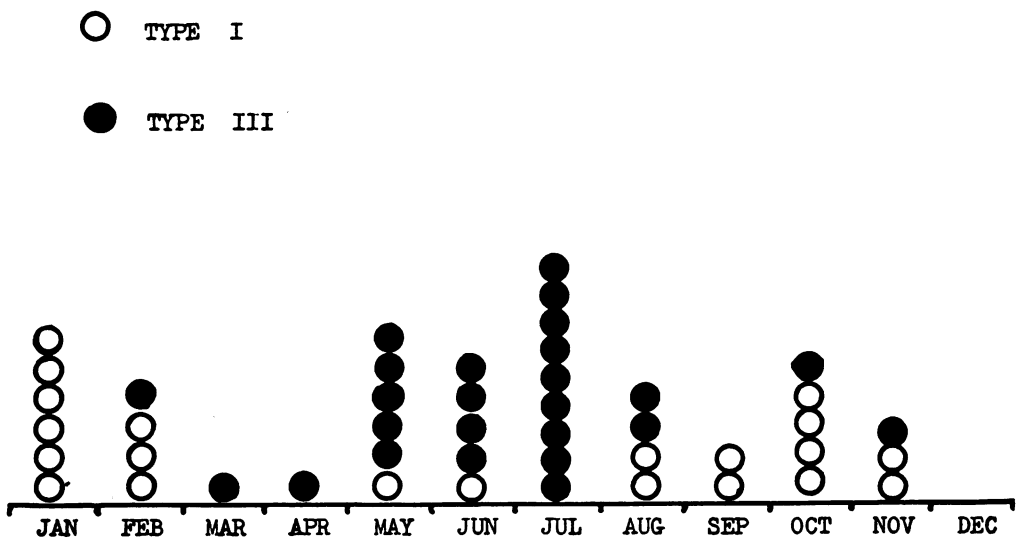

Fig. 1—Number of poliovirus isolations each month during 1958.

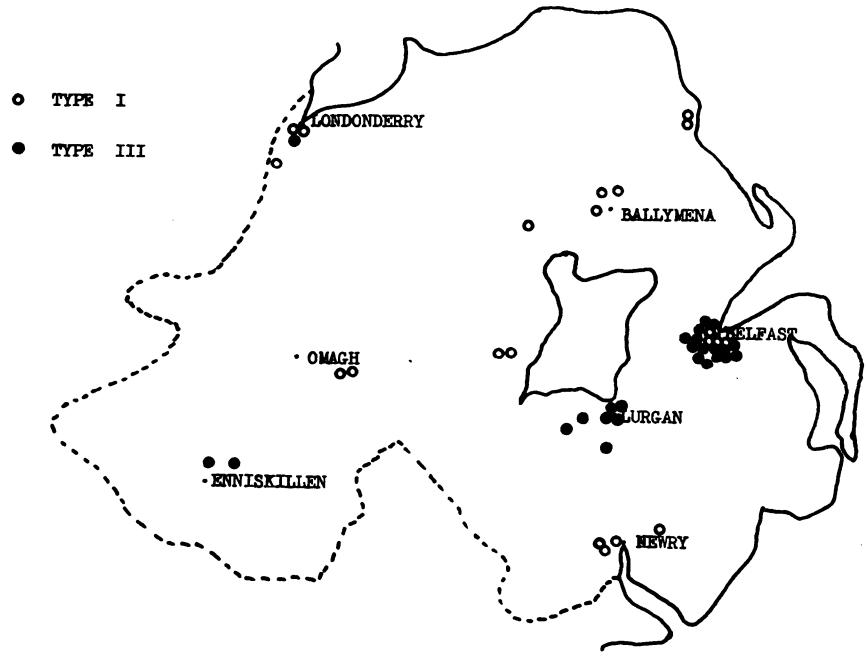

Fig. 2—Geographical distribution of individuals from whom poliovirus isolated.

It may be seen that the type 3 virus infections were practically entirely confined to the Lagan valley, and that, apart from that area, there were only a few sporadic cases in other parts of Northern Ireland.

Poliomyelitis Vaccine Surveillance.

Two cases of poliomyelitis have been recorded in vaccinated children during 1958. One of these was an infant of ten months with agamma-globulinæmia who became paralysed on 20th August, and from whom type 3 poliovirus was isolated. This infant had been given its first inoculation with formalinized vaccine in May and the second in June. The other was an eighteen-month-old child who developed paralysis on 11th August. He had been immunized with formalinized vaccine in March and April, 1958. Type 3 virus was also isolated from this child.

These findings do not constitute a break in safety, nor is there any question that the vaccine used was unsafe. Such cases serve as a reminder that the currently available vaccine does not give protection to more than 70 to 80 per cent. of immunized individuals.

TABLE 2.

SHOWING ETIOLOGY OF ASEPTIC MENINGITIS IN 1958.

CLINICAL DIAGNOSIS	NO. FROM WHOM FÆCAL SPECIMENS OBTAINED	NO. FROM WHOM VIRUS ISOLATED					NO. FROM WHOM SUITABLE BLOOD SAMPLES	NO. WITH SEROLOGICAL EVIDENCE OF MUMPS VIRUS
		Polio. Type 1	Polio. Type 2	Polio. Type 3	Echo Virus	Coxsackie Virus		
"Non-paralytic Polio" - - -	38*	2	0	2	1	1	11	4
"Lymphocytic or Aseptic Meningitis"	50	0	0	1	1	1	37	15
TOTAL ASEPTIC MENINGITIS -	88	2	0	3	2	2	48	19

*Including eight notified cases of "non-paralytic poliomyelitis."

Aseptic Meningitis.

In addition to the eight notified cases of "non-paralytic poliomyelitis," specimens were received from thirty patients with a provisional diagnosis of "non-paralytic poliomyelitis." These are considered as cases of aseptic meningitis, which is a much preferable diagnostic term and also includes the clinical term "lymphocytic meningitis." Indeed, it has been recommended by the World Health Organization (1958) that notification of "non-paralytic poliomyelitis" should not be made and that the term *aseptic meningitis syndrome (etiology unknown)* be used until the etiological agent has been identified when the diagnosis *aseptic meningitis syndrome (poliovirus type 1, 2 or 3)*, *aseptic meningitis syndrome (ECHO virus)*, etc., can be made.

It may be seen (Table 2) that the commonest identified cause of aseptic meningitis during 1958 was mumps virus. Poliovirus was isolated from only five of eighty-seven specimens examined (5.7 per cent.), which is in contrast to 1957—a poliomyelitis epidemic year—when 41 per cent. of cases of aseptic meningitis were found to have type 1 poliovirus in their fæces.

TABLE 3.

SHOWING ETIOLOGICAL IMPORTANCE OF MUMPS VIRUS IN C.N.S. INFECTIONS IN NORTHERN IRELAND DURING 1958.

CLINICAL DIAGNOSIS	No.	No. WITH SEROLOGICAL EVIDENCE OF INFECTION WITH / No. FROM WHOM SUITABLE BLOOD SAMPLES OBTAINED		
		Mumps	Louping Ill R.S.S.* Encephalitis	Lymphocytic Choriomeningitis
Mumps Encephalitis	21	16/21	0/21	0/21
Encephalitis	47	5/20	1/45	0/45
Aseptic Meningitis	102	19/48	0/77	0/77
TOTAL	170	40/89	1/143	0/143

*Russian spring summer.

Encephalitis.

Mumps encephalitis (Table 3) was quite frequently diagnosed clinically during 1958 and Dr. C. M. B. Field (personal communication) told us that he has never before seen so many cases of meningo-encephalitis associated with mumps. Although the clinical picture of uncomplicated mumps has not changed since the time of Hippocrates (see Adams, 1891), it seems that from time to time there is a change in the neurotropism of the virus or in the host which leads to involvement of the C.N.S. In addition to the patients diagnosed as having mumps encephalitis, five patients with encephalitis of possible viral etiology were shown to have infection with mumps virus. It may be seen from Table 3 that, including the patients with a clinical diagnosis of aseptic meningitis, there was a total of forty infections with mumps virus giving rise to C.N.S. signs and symptoms.

The seasonal distribution of the forty cases of mumps encephalitis are shown in Fig. 3.

Encephalitis due to louping ill/Russian-spring-summer encephalitis virus was established in one case of encephalitis and type 3 poliovirus was recovered from another. In the louping ill infection the patient was a farmer, aged 24, who had removed a tick from his shoulder two days before the onset of his illness, and had been shearing sheep ten to fifteen days before this. The serum from this patient was the only one to give a positive result against louping ill/Russian spring-summer encephalitis virus out of one hundred and forty-three tested during 1958.

Other C.N.S. Infections.

In none of one hundred and forty-three patients tested was there evidence of infection with the virus of *Lymphocytic choriomeningitis* (L.C.M.). Indeed

no infection with L.C.M. has been diagnosed in Northern Ireland since the Virus Reference Laboratory started investigations.

In addition to the cases of paralytic poliomyelitis notified to the Ministry and clinically confirmed (Table 1), specimens were received from twenty patients in whom a provisional diagnosis of paralytic poliomyelitis had been made. No poliovirus or other enteric virus was isolated from fæcal samples from any of these patients nor was there any evidence that they had had recent infections with mumps, louping ill or L.C.M. viruses.

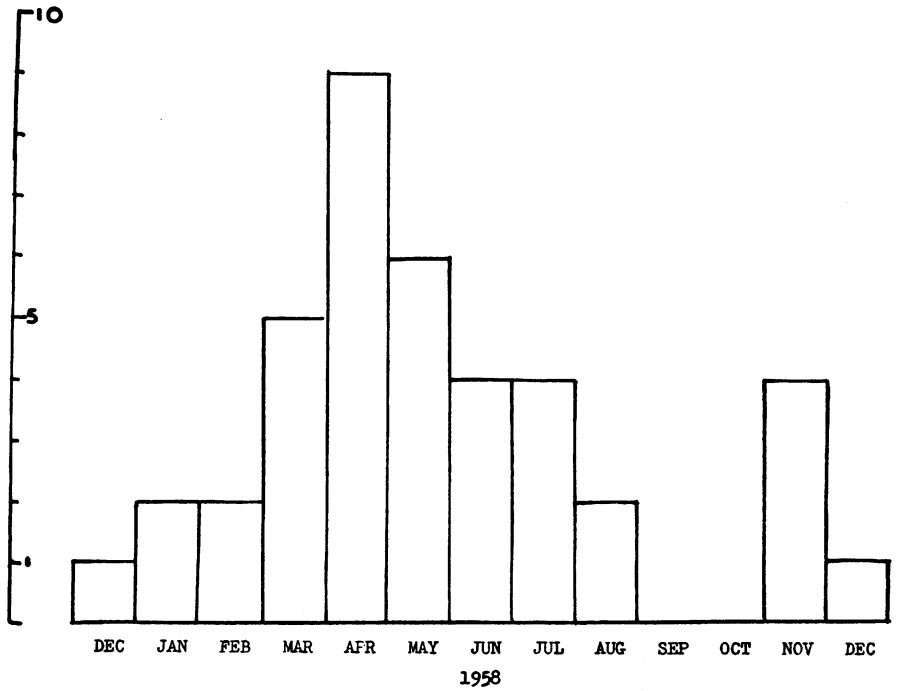

Fig. 3—Monthly incidence of mumps meningo-encephalitis confirmed by laboratory tests.

Miscellaneous Isolations of Enteric Viruses.

As seen from Table 2, two ECHO viruses and one Coxsackie virus were isolated from cases of aseptic meningitis. Studies are in progress to establish the ætiological importance of the ECHO and Coxsackie group of viruses recovered during the past four years in aseptic meningitis and other conditions (see Report, 1957). The identification of these viruses to date, from cases of aseptic meningitis, is shown in Table 4.

During 1958 Coxsackie A9 virus was also isolated from two patients with a clinical diagnosis of Stevens-Johnson syndrome and exfoliative dermatitis respectively. There is as yet no evidence that this virus has anything to do with the etiology of these infections.

In addition to the isolations of poliovirus for diagnostic purposes re-isolations of type 1 virus were made in a paralytic patient during convalescence, and two strains of type 3 were made from contacts of paralytic patients.

Respiratory Virus Infections.

Influenza

As part of the World Health Organization influenza spotting scheme, the laboratory continued attempts to detect the presence of influenza virus in the community with the collaboration of a number of general practitioners. During

TABLE 4.

Showing Enteric Viruses other than Poliovirus isolated from Fæces of Patients suffering from Aseptic Meningitis Syndrome.

Virus	1955	1956	1957	1958
ECHO 3	–	–	–	1
ECHO 6	–	–	–	1
ECHO 9	–	3	11	–
Coxsackie A9	–	–	1	1
Coxsackie B2	–	–	1	–
Coxsackie B3	–	–	2	–
Coxsackie B4	7	–	–	–
Miscellaneous Enteric Viruses*	4	1	4	2

*These viruses cannot, at the moment, be classified.

1958 influenza virus was isolated only during January and March. A total of eight strains of virus were recovered, of which six were typed and found to be A (Asian) strains. Excluding the eight patients from whom virus was isolated, the following tests were made on patients' sera for evidence of recent infections with influenza virus.

Virus	No. Tested	No. Positive
Influenza A	76	0
„ B	70	0
„ C	3	0

It may be concluded that the influenza viruses played only a small part in causing influenza-like illness during 1958.

Adenovirus Infections.

Sera from sixty-four patients were tested for adenovirus infections. Only one case was diagnosed by a rise in antibody in paired sera. The patient was a young doctor who had symptoms of rhinorrhœa, conjunctivitis, and headache. Thus,

during 1958 as in 1957, adenoviruses appear to have been an uncommon cause of respiratory infections in Northern Ireland.

Psittacosis.

Sera from one hundred and twenty-nine patients were tested against the psittacosis group of viruses with negative results. To date, sera from two hundred and sixty-seven individuals in Northern Ireland have been tested with no evidence of any recent infections with psittacosis or related viruses.

Special Investigations.

Dermatological Investigations.

In collaboration with Dr. J. M. Beare attempts have been made to isolate an infective agent from *pityriasis rosea.* These studies have so far been negative. We are anxious to see patients with this condition at the earliest stage of onset when the "herald spot" is present and before the onset of the rash, and we shall be grateful for the co-operation of general practitioners in this. Studies have been made in tissue culture of material from a number of cases of *molluscum sebaceum* without providing evidence on the nature of this condition.

Abortions.

In Belfast during 1957 more than 10 per cent. of pregnancies did not go to term, and there are over one thousand abortions each year in the city (Mr. H. I. McClure, personal communication). There are several viruses which are known to cause abortion in domestic animals, and the possibility that viruses might be responsible for some human cases of abortions prompted the following investigation. Attempts were made to isolate virus, in the yolk sac of developing chick embryos and in HeLa cells, from the conceptum of twenty-two selected individuals. The results were entirely negative, nor was there any serological evidence of past or recent infection with the enzootic abortion-psittacosis group of viruses.

Complement Fixation Test in Poliomyelitis.

The possibility of using the complement fixation test (C.F.T.) in the diagnosis of acute poliomyelitis has been investigated. We concluded that this test is of less value in the prompt and accurate diagnosis of the disease than virus isolation from fæcal specimens. A similar conclusion has been reached by several American virologists working on the same problem.

The C.F.T. is of some value in diagnosis when no virus has been isolated. We have used it in the investigation of special cases such as those following inoculations where a diagnosis, even though it is late, may be of public health importance.

The 1957 epidemic of poliomyelitis in Belfast has been the subject of close study by members of this department and also by Dr. S. N. Donaldson of the Belfast City Health Department. In this study (to be published) the C.F.T. was of considerable value in arriving at an accurate diagnosis in the few cases of possible poliomyelitis from whom no virus was isolated.

Budgerigars and Poliomyelitis.

The reported isolation of poliovirus type 1 from a sick budgerigar in a household in Scotland where a child had died of poliomyelitis by Somerville, *et al.* (1958), prompted an investigation of the possibility that budgerigars might play a part in the epidemiology of some cases of poliomyelitis. The result of this study, which has been published (Dane, Dick & Donaldson, 1959), indicates that it is most unlikely that budgerigars play any part in the natural history of poliomyelitis.

Discussion.

In addition to the tests recorded above a large number of miscellaneous specimens were sent for virus studies. Specimens sent from many patients were such as to make it impossible for the laboratory to give any diagnostic help. While virus isolation provides the most useful rapid result for some diseases such as poliomyelitis and other enteric viruses, in the diagnosis of many other infections serological tests are more convenient. For serological diagnosis, two samples of clotted blood are required, which are usually referred to as paired sera. The first sample should be taken as soon as possible during the acute phase of illness and the second sample two to three weeks later. Unfortunately with presently available techniques it is seldom that a diagnosis can be made on a single serum. We and many physicians have been perhaps disappointed in our failure to produce an answer in some infections, but very often the reason has been that only a single late specimen of blood has been available. It is certain that with suitable specimens more infections would have been diagnosed. In a previous number of this Journal detailed information on the types of specimens which are required for virological studies was given (Dick and Dane, 1958).

A number of specimens were received from patients with infective hepatitis. There is as yet no virological test for virus hepatitis, and we now have an adequate supply of infective hepatitis material for research purposes.

We hope this year to undertake studies on the viral etiology of glandular fever and are anxious to obtain throat swabs, fæcal and blood samples from patients with this illness. We would also be grateful for co-operation in obtaining throat swabs and blood samples from patients with german measles and from small children with respiratory illnesses in which a number of newly discovered viruses have been recently reported.

We wish to acknowledge the co-operation which we continue to have from the staff of the Northern Ireland Fever Hospital, from the pathologists and other consultants in Northern Ireland and from the College of General Practitioners and Medical Officers of Health.

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CO-EXISTENT TUBERCULOSIS AND CARCINOMA OF THE LUNG

By **G. H. B. BAKER, M.B.**

Department of Pathology, Queen's University, Belfast

THE co-existence of pulmonary tuberculosis and bronchial carcinoma has been commented on many times and many authors have assessed the relative ætiological importance of the one to the other. It has, for example, been held (Rokitansky, 1854) that tuberculosis and carcinoma were antagonistic, whereas Ewing (1931) believed that tuberculosis was the main ætiological factor in carcinoma of the lung.

A recent routine post-mortem showed both conditions and this led me to undertake a study of the records of the Department in an attempt to assess the significance of their co-existence.

RESULTS.

In the 13,000 autopsies recorded between 1937 and July, 1958, there were 357 cases of bronchial carcinoma. Of these there were twelve cases of active pulmonary tuberculosis. The post-mortem findings in these twelve cases are summarised below:—

(1) M.62: Squamous metaplasia of bronchus with resultant carcinoma of the left upper lobe. There was co-existent fibro-caseous tuberculosis of the left upper lobe.

(2) M.61: Tuberculous cavitation of the left upper lobe with a squamous carcinoma in the wall of the cavity.

(3) M.59: Anaplastic carcinoma of the right lung with a mild degree of active tuberculosis of the left lung.

(4) F.58: Squamous carcinoma of the left main bronchus with extensive fibro-caseous tuberculosis of the left lung.

(5) M.64: Tuberculous cavitation of the right upper lobe with an anaplastic carcinoma in the wall of the cavity.

(6) M.51: Anaplastic carcinoma of the left main bronchus with a microscopic active tuberculous complex in the left lung.

(7) M.47: Anaplastic carcinoma and active tuberculosis intimately mixed in the right lung. Tuberculous cavitation of the left apex.

(8) M.62: Anaplastic carcinoma of the left main bronchus with fibrosis and cavitation at the left apex.

(9) M.51: Widespread adenocarcinoma arising in the right upper lobe bronchus and intimately mixed with caseating bronchopneumonia.

(10) M.76: Peripheral squamous carcinoma in the right lung and caseating bronchopneumonia of the right lung.

(11) M.67: Squamous carcinoma of the right upper lobe bronchus with caseating bronchopneumonia of the right lung.

(12) M.65: Microscopic anaplastic carcinoma, side not recorded, with tuberculous cavitation at the right apex.

To summarise, these are twelve cases showing co-existent pulmonary tuberculosis and bronchial carcinoma. In one of these cases the lesions were on different sides. In one the carcinoma was a microscopic lesion and the side not recorded. In a third, tuberculosis was present on both sides, but the more active lesion was on the side of the carcinoma. In the other nine the carcinoma and the active tuberculosis were on the same side. In three of these the carcinoma appeared to be related to the chronic infective process, two of them arising in the walls of cavities and one in a bronchus which was the site of squamous metaplasia due to chronic infection. In the other six cases, and in the case where the tuberculosis was more active in the lung which also showed carcinoma, it seems likely that the bronchial carcinoma played a part in the localisation of the tuberculous process in the section of the lung distal to it.

In an attempt to discover whether carcinoma caused a different incidence of tuberculosis, 357 records were studied of post-mortems on males over fifty years in the period reviewed. Eight of these showed active tuberculosis and this does not seem statistically different from the incidence found in cases with carcinoma. However, the tuberculosis did not appear to be as fulminant, on average, in these control cases.

Discussion.

Several factors may contribute to the finding that pulmonary tuberculosis and bronchial carcinoma, when they occur in the same patient, are very likely to occur in the same lung. The most obvious is that squamous metaplasia may occur as a result of the chronic inflammatory process and may undergo a malignant change. A second factor is probably the erosion of the fibrous encapsulations of quiescent tuberculous foci by the carcinoma, with resultant dissemination of organisms through that lung. A further factor is concerned with the effect of the carcinoma on the bronchus. There it exerts a profound effect upon the lung distal to it, distorting the dynamics of its air flow, preventing normal ciliary drainage upwards, and possibly interfering with blood and lymph circulation to the lobe concerned. All these factors certainly reduce the resistance of the lobe to infection and it is well known that bronchopneumonia is a common complication of carcinoma because of these factors. In the same way, if there are any tubercle bacilli in the region, they may multiply and cause severe infection more easily under these conditions.

The co-existence of the two conditions is becoming more common, both because of the increased incidence of bronchial carcinoma and because of the older age group in which tuberculosis is now occurring. This fact lends even

greater clinical importance to this interesting problem. Clinically, the problem obviously arises in two different ways. In hospitals for chest diseases the tuberculosis is recognised, and in general hospitals, as in this series, the carcinoma tends to be recognised. In either hospital the ante-mortem diagnosis of both conditions is rare, though Gerstl, *et al.* (1946), was able to diagnose both several times in a sanatorium. In the known presence of tuberculosis the following circumstances may suggest co-existent carcinoma:—

(1) Failure of the tuberculosis to resolve as quickly or as completely as expected under the normal chemotherapeutic and sanatorium regime.

(2) A unilateral increase in size of the hilar lymph nodes on radiological examination (Rigler, *et al.*, 1959).

If carcinoma is suspected, for these or other reasons, bronchoscopy must be carried out. In the known presence of carcinoma, tuberculosis must be suspected if a supposed acute bronchopneumonia does not subside rapidly on treatment with the correct antibiotics, etc. Even in the absence of this finding it is worth culturing the sputum for tubercle bacilli, but if any suspicion exists multiple sputum examinations are imperative.

Finally, the danger of tuberculous infection among the contacts of these patients must be remembered. Hence, if a patient should die with the tuberculosis undiagnosed and so not noted on the death certificate, the tuberculosis authorities should be informed if active tuberculosis is found at post-mortem.

Summary.

In twelve cases of co-existent active pulmonary tuberculosis and bronchial carcinoma the lesions were on the same side in ten. In one the side of the carcinoma was not recorded. The incidence of active tuberculosis in cases with carcinoma was not statistically different from cases without carcinoma. It seems likely that carcinoma may occasionally arise in a lung already the site of a tuberculous cavity.

It is suggested that the existence of a bronchial carcinoma may increase the fulminance of a tuberculous lesion in the affected lung. Some factors involved in this relationship are discussed. The increasing clinical importance of the problem is stressed and some suggestions are made as to how one condition may be suspected in the known presence of the other.

I wish to thank Professor J. H. Biggart for his help in the preparation of this article.

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REVIEWS

PRESENT STERILIZING PRACTICE IN SIX HOSPITALS. (Pp. 75. 5s.) London: The Nuffield Provincial Hospitals Trust, 1958.

THERE has been prominence recently in the medical press on sterilization methods in hospitals, and it is becoming increasingly recognized that all is not well with steam-pressure sterilizers and sterilization procedures in many of our hospitals.

This report by an operational research team of the Nuffield Provincial Hospitals Trust, on sterilizing practice in six British hospitals, observed over a period of eighteen months, does nothing to allay misgivings about the widespread inefficiency of equipment and procedures. The six hospitals selected for the investigation were a London teaching hospital, three provincial hospitals, and two cottage hospitals. Sterilizing procedures were observed and autoclaves were tested, and the report indicates the need for hospital authorities to examine as a matter of urgency existing equipment and present methods of sterilization in wards, operating theatres, and autoclave rooms.

In the section dealing with hospital wards, "utility rooms" are criticized—too near to wards, used for disposal of soiled dressings, inadequate storage accommodation, contamination of dressing drums, instrument dishes, and Cheatle forceps from open windows and excessive traffic. Many drums were found to be unsatisfactory due to perforation and damage to lids, catches, hinges, and ports; linings were unsuitable, and not laundered or replaced regularly, and some drums were too tightly packed. Twenty-nine out of 161 (18 per cent.) swabs taken of sterilized equipment were found to be unsterile. Bed-pan washing was unsatisfactory, but has a satisfactory bed-pan washer that washes *and* cleanses yet been designed? The various methods used to pack and sterilize syringes left much to be desired and a Central Syringe Service is strongly recommended.

In operating theatres some structural and ventilating defects are noted, with infrequent washing of walls and fixed equipment. Theatre staff were, however, found to be more sterilization-minded than ward staff.

Sterilizing equipment and practice in the autoclave room are severely criticized—bad siting, unhygienic conditions, poor ventilation, unsuitable personnel, and lack of responsible control. Out of seventeen large autoclaves tested eight were functioning satisfactorily, four were of doubtful efficiency, and four were clearly unsatisfactory. The main causes of inefficiency were faulty installation, or more commonly faulty operation. One of the most unsatisfactory features of autoclaves was air filtration, and the finding that 38 per cent. of swabs taken from the inside of sterilized drums yielded bacterial growth is attributed to recontamination after sterilization.

After having detailed the many serious faults in current sterilizing practice, the report deals in the final section with recommendations for immediate improvements which may be introduced at no great cost, and without prejudice to long-term planning. The six main proposals are—(1) To improve the working of existing autoclaves; (2) to eliminate hospital drums and introduce a substitute (the team recommends cardboard cartons, but not all would agree, and it is surprising that there is no mention of packs wrapped in a double layer of fabric, universally employed in the United States and now coming into use in this country; (3) to improve methods for sterilization of syringes; (4) to raise the standard of current sterilizing practices; (5) to better the methods for (*a*) the disposal of dirty dressings and linen, and (*b*) providing bed-pans which are socially clean; and (6) to define responsibility.

The report contains many photographs of defective equipment and ward scenes which illustrate some of the faults and problems.

This report gives much food for thought, and should be read by all concerned with hospital sterilization equipment and practices and the supervision thereof—this includes medical nursing, engineering, and administrative staff. V. D. A.

PRACTICAL CLINICAL BIOCHEMISTRY. By Harold Varley, M.Sc., F.R.I.C. Second Edition. (Pp. vii + 635; figs. 78. 42s.) London: Heinemann, 1958.

SINCE publication in 1954 of the first edition of "Varley" it has become a standard laboratory text for all clinical biochemists. It is, therefore, most gratifying that in this second edition the work is brought up to date without any sacrifice of those characteristics which made such an impression in 1954. The book contains all the methods that a clinical chemist could expect to use in a teaching hospital laboratory in sufficient detail to enable them to be set up without reference in most cases to the original article. In spite of this, each section is provided with an extensive bibliography for those seeking information. The opening sections on the collection and preparation of specimens is particularly useful as is the appendix on volumetric standards, indicators, and buffers.

The new material in this edition is the hormone section, an account of the hydroxyindoles and one of the transaminases. The treatment of electrophoresis has been completely expanded and now forms a valuable description of the available techniques. All this new material is of the high standard which is a constant feature of this text.

There are, however, criticisms of detail. Present-day laboratory practice has led to the almost complete abandonment of visual colorimeters and it seems unnecessary to perpetuate them in what is virtually a new work. It is also hardly in keeping with modern practice to continue to describe methods for fæcal fat estimation based on the use of dried fæces. In an attempt presumably to keep down the cost of the book, the quality of the paper used is very poor and might not be sufficiently serviceable for a book which will be in regular use at the bench. The reviewer's copy also contained one section which had been inadequately bound and became free at the first reading.

These minor criticisms do not, however, detract materially from what is undoubtedly one of the most valuable laboratory textbooks in this subject. D. W. N.

AIDS TO NEUROLOGY. By E. A. Blake Pritchard, M.A., M.D., F.R.C.P. Second Edition. (Pp. 480; illustrated. 15s.) London: Baillière, Tindall & Cox, 1959.

THIS is the second edition of a book which was first published in 1932. It is the author's intention to "provide an introduction to the basic essentials of neurology for students in the earlier years" of their training. He believes that a knowledge of anatomy and physiology is subordinate to clinical observation and that in the majority of nervous disorders the symptoms cannot be explained in terms of well-defined disturbances of physiology. As a result of this policy the clinical description of disease is more detailed than might be expected in a book of this size, but anatomy and physiology are relegated to the last chapter, and clinical methods are found in an appendix of five pages.

However suitable this lay-out may have been twenty-seven years ago, the reviewer feels that more account might have been taken of current opinion on medical education in which the preclinical sciences are designed to lay a firm foundation for clinical practice.

The facts are presented in a relatively dogmatic manner and there is little or no speculative discussion. One or two misleading statements are to be found. The most obvious example in a table showing the relative incidence of "cerebral tumours" (where the author is clearly referring to "intracranial tumours") expressed in percentages (notwithstanding that the given figures add up to 117). In this table pituitary gland neoplasms comprise 20 "per cent." of all tumours. No warning is given that this figure is exceptionally high because it was taken from the experience of Hanvy Cushing, who, owing to his particular interest in this field, attracted a greater proportion of patients with pituitary tumour than would be seen in a general hospital.

The text is readable with no attempt at economy in words, and clarity is enhanced by paragraph headings and enumerated lists of salient points.

Prospective purchasers should not be deceived by the apparent size of this book, for it contains no less than 150,000 words, which may be compared with 180,000 words in the other famous textbook of neurology emanating from University College Hospital.

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The facts are presented in a relatively dogmatic manner and there is little or no speculative discussion. One or two misleading statements are to be found. The most obvious example in a table showing the relative incidence of "cerebral tumours" (where the author is clearly referring to "intracranial tumours") expressed in percentages (notwithstanding that the given figures add up to 117). In this table pituitary gland neoplasms comprise 20 "per cent." of all tumours. No warning is given that this figure is exceptionally high because it was taken from the experience of Hanvy Cushing, who, owing to his particular interest in this field, attracted a greater proportion of patients with pituitary tumour than would be seen in a general hospital.

The text is readable with no attempt at economy in words, and clarity is enhanced by paragraph headings and enumerated lists of salient points.

Prospective purchasers should not be deceived by the apparent size of this book, for it contains no less than 150,000 words, which may be compared with 180,000 words in the other famous textbook of neurology emanating from University College Hospital.

TEXTBOOK OF PHYSIOLOGY AND BIOCHEMISTRY. By G. H. Bell, J. N. Davidson, and H. Scarborough. Fourth Edition. (Pp. xi + 1065; illustrated. 63s.) Edinburgh and London: E. & S. Livingstone, 1959.

SINCE first published in 1950 new editions of this textbook have appeared regularly at three yearly intervals and have won for the book a place of high preference among undergraduate medical students. The reasons for this popularity are clear. The combined efforts of a biochemist, a physiologist, and a clinician have led to a very balanced and up-to-date account of the fundamentals of physiology and biochemistry in a single volume. There is a refreshing emphasis on human physiology. The standard of illustration is excellent and there are many beautiful records and graphs which should encourage the student to think of physiology in terms of experimental evidence. The text is extremely readable and clear and is very rarely split by headings and sub-headings. The latter may account for the book's lesser popularity among postgraduate students reading for higher degrees, who might prefer more classification of the text to facilitate quicker revision and reference.

The present edition retains the character and style of the earlier editions, though in an attempt to keep up to date portions of many chapters have been rewritten and some new illustrations, including a few in colour, have been added. This has fortunately been achieved without an increase in bulk. In fact, the present edition is three pages shorter, though three shillings dearer than the third edition. I. C. R.

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THIS book is written by one of our leading pharmacologists to serve as an introduction to the romantic science of pharmacology and it is meant, I think, mainly for students who intend to be true pharmacologists rather than doctors.

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One excellent feature of this book is that each chapter begins with a concise and interesting account of the experimental methods by which pharmacologists investigate the properties of drugs. Another excellent feature which I wish were copied by many other authors is the bibliography which is given on pages xiii to xvi and the frequent text references to original papers or reviews. O. L. W.

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With these reservations, this book, which is written in a readable conversational style, can be recommended as providing a good general introduction to neo-natal pædiatrics. I. J. C.

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Beginning with a historical survey, succeeding chapters deal with taxonomy, morphology, metabolism, antigenic structure, staphylophages, coagulase hæmolysins, and other diffusible products, which combine to make up one of the most complex and protean bacterial pathogens. The adaptability of the Staphylococcus to antibiotics and other environmental conditions is fully described, and other chapters are devoted to virulence and disease, and immunity.

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TEXT BOOK OF SURGERY. By Patrick Kiely, B.Sc., M.D., M.Ch., F.R.C.S. Second Edition. (Pp. 1148; figs. 605. £3. 3s.) London: H. K. Lewis, 1958.

THE author sets out to write primarily for medical students, covering all aspects of surgical practice, the emphasis being on clinical features and diagnosis. Treatment is outlined and no attempt is made to give details of operative procedures. Many subjects are classified in the form of lists of causes, etc.; for example, the section on affections of the nipple gives twelve causes and each is described in turn. This example shows something of the detailed nature of the work, which runs to 1,148 closely printed pages.

A minor criticism is that the illustrations are few—the insertion of more would undoubtedly help the student to understand better the diseases he reads about in the text. Fluid balance should be considered in greater detail.

None the less, it is a most comprehensive work, a good book of reference complete with index, and the information it contains gives a balanced view of present-day surgical practice.

A. MCC.

A CLINICAL INTRODUCTION TO HEART DISEASE. By Crighton Bramwell, M.A., M.D., F.R.C.P. (Pp. vii + 229; figs. 61. 21s.) London: Oxford University Press, 1959.

EVERY doctor who has charge of cardiac patients should read this book. Its 218 pages contain a mine of common sense in the diagnosis and management of the cardiology of every-day practice. Emphasis is placed on clinical assessment, and various techniques, more in the realm of the specialist, are used more by way of illustration. The author's personal approach to the patient, which is of great interest, is illustrated by specific case histories. In general, the adult patient receives more attention than the congenital lesions usually seen in pædiatric practice. The text is pleasantly readable. There is a good index, and the size of book commends it. The general practitioner will specially welcome this book. It may be said to have been written for him by an author with a lifetime experience of his subject. The book deserves to be widely read.

E. F.

BIGGER'S HANDBOOK OF BACTERIOLOGY. By F. S. Stewart, M.D.(Dublin), F.R.C.P.I. Seventh Edition. (Pp. 611; figs. 92; plates 3. 37s. 6d.) London: Baillière, Tindall & Cox, 1959.

PROFESSOR STEWART, Professor of Bacteriology and Preventive Medicine in Dublin University, has, after a lapse of ten years, brought out the seventh edition of Bigger's Handbook of Bacteriology and he has endeavoured to preserve its original character in spite of the fact that the amount of new knowledge available since 1949 is very large. This applies particularly to the viruses and, in order to include adequate information about them, Professor Stewart omitted the chapters on fungal and protozoal infections which were in the previous editions. In spite of this omission, the book contains six hundred pages and is by no means a small volume, since, because of new knowledge, practically three-quarters of the text has had to be rewritten. Indeed it would be useful to the practising physician as a book of reference since it is up to date, clear, and comprehensive enough to meet most of their requirements.

From the point of view of the average medical student, the book would be more useful if it were shorter and if the sections on fungi and protozoa had not been left out. These two subjects seem to be the poor relations of the viruses and bacteria but in ordinary practice they are not of negligible importance and the student should be introduced to them at some stage in the undergraduate career.

The systematic description of the various bacterial genera has been done most competently. Streptococci and C. diphtheriæ are particularly fully dealt with but one might suggest that a little more emphasis could have been placed on the rôle of the staphylococcus pyogenes in the problem of cross infection in hospitals.

It may be correct to label the Cl. Welchii "Cl. perfringens," but in spite of Bergey, the name C. Welchii is the better known and more commonly used one.

The chapter on the general properties of viruses gives the student just the information necessary and the whole section on virology is to be recommended not only for students but for those members of the profession who wish to be brought up to date as painlessly as possible.

The reviewer found very few mistakes but, incidentally, Dr. Likar's name is as written.

The book is easy to read, pleasant to handle, well produced, and the illustrations are good, but the inclusion of some more figures and graphs would have been an advantage especially in the section on immunology.

Previous editions of this work have been very popular with students and this new edition is a worthy successor to those that have preceded it. It might also be described as a fitting memorial to the late Professor Bigger, who, as he stated in his preface to the first edition, always had his students' welfare uppermost in his mind. E. O. B.

CARDIOVASCULAR SOUND IN HEALTH AND DISEASE. By Victor A. McKusick, M.D. (Pp. xii + 570; illustrated. 120s.) London: Baillière, Tindall & Cox, 1959.

THIS book is a monumental work covering all aspects of the vibrations produced by the movements of the structures of the heart during the cardiac cycle in health and disease. Respiratory sounds are also covered. There are nine sections, each devoted to a particular theme of the subject. The historical survey in section one should be read by all doctors—it is comprehensive and intensely interesting, and relates some of the lighter side of the Paris of Lænnec, when that city led the world in cardiological clinical research. However, the cardiologist is likely to derive most benefit from the book. The technique of spectral phonocardiography, as developed by the author, is expounded. The sections on the systematic presentation of heart sounds in particular aspects of heart disease, such as valvular lesions and congenital lesions, are particularly useful for clinical assessment, and are a valuable source of reference for special information in the subject. The research worker will require this book. It is well indexed, and there are over 1,600 references. The book is produced in good quality glazed paper, and the type is clear. Its 506 pages contain a mine of information, which every library should provide. E. F.

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CYCLOPROPANE ANESTHESIA. By Benjamin Howard Robbins, B.A., M.S., M.D. Second Edition. (Pp. xii + 293; illustrated. 72s.) London: Baillière, Tindall & Cox, 1958.

DR. ROBBINS' book first appeared in 1939, containing 165 pages and listing 206 references. In the new edition these have increased to 286 pages with 353 references. One new chapter on the relaxant agents appears in the latest issue, otherwise the format is unchanged from the first edition.

There is much useful information in this book, but it is very difficult to know whether it is intended for reading by pharmacologists or by practising anæsthetists. The first chapter deals admirably with the physical properties of cyclopropane, but ends with the astonishing statement, "All anæsthetics except N_2O and CH, Cl_3 are explosive in anæsthetic concentrations." British anæsthetists who have used trichlorethylene for many years with great success, and who are now becoming acquainted with halothane, would never agree with this.

If the book is to be of use to anæsthetists, the second chapter should discuss the effect of cyclopropane on the central nervous system, which, after all, is the reason for its present clinical use. Instead of this we are given an enormous amount of data from various sources on the concentrations required for anæsthesia. This is, in places related to the clinical depth of anæsthesia or the E.E.G. pattern of depression without a description of how either of these is classified. In a book of this type, it is not sufficient to present the data of various different authors in animal and human experiments without critically evaluating their work, correlating their findings, and attempting to explain the discrepancies of the results of different workers.

By far the most useful section is that dealing with the action of cyclopropane on the cardiovascular system, but even in this many of the above criticisms still apply. Emphasis is laid on the prophylactic value of barbiturate premedication on the prevention of cardiac arrhythmias with less attention to the importance of maintaining an adequate respiratory exchange and elimination of carbon dioxide during anæsthesia. This latter has been established as a major factor in the initiation of arrhythmias (via the sympatho-adrenal system) for many years.

There is an extremely good description of the technique of induction of anæsthesia with cyclopropane and oxygen, yet the sequence of events when cyclopropane is used after an initial dose of thiopentone is barely mentioned. In this same section on anæsthetic techniques the history of CO_2 absorption is dealt with fully; however, no data is given on the efficacy of the various circuits or chemical absorbents in present clinical use. Since cyclopropane must be used in a closed circuit, this is a grave omission if the book is to be of use to practising anæsthetists. Likewise, although the pharmacology of the muscle relaxants is discussed in detail, the influence of these drugs on the clinical use of cyclopropane is ignored.

It is remarkable to find that less than 10 per cent. of the 353 references come from British journals and only two from anæsthetic journals published in this country. Furthermore, a large number of the British references are to muscle relaxants or to some topic completely unrelated to cyclopropane. This lack of balance in choice of references must of necessity distract from the value of this monograph to the clinicians in this country, and while it is useful as a reference book the price of necessity limits its purchase largely to medical libraries.

J. W. D.

BLOOD PRESSURE SOUNDS AND THEIR MEANINGS—PART 2: ÆTIOLOGY OF MELANOTIC CANCER. By John Erskine Malcolm, B.Sc., M.B., B.Ch., F.R.C.S. (Pp. v + 70; figs. 14. 12s. 6d.) London: Heinemann Medical Books, 1959.

THIS small book will only appeal to a few. It is difficult to comprehend, embracing as it does abstruce mathematical formula, complicated biochemical dynamics, and engineering principles—all in 63 pages. Certainly it contains original ideas, but experimental results would be more convincing than philosophical conceptions. Read this book if you will, but be prepared for deep thought and be prepared for hard work if you decide to pursue the author's ideas. He has an extensive reference for this compact account of the nature of things. E. F.

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BRITISH OBSTETRICAL AND GYNÆCOLOGICAL PRACTICE: GYNÆCOLOGY. Edited by A. W. Bourne, F.R.C.S., F.R.C.O.G. (Pp. xii + 891; illustrated. 105s.) London: Heinemann Medical Books, 1958.

THE new edition of British Gynæcological Practice has been eagerly awaited. There have been improvements since the last edition and the book has been brought up to date. Most sections are very well written, easy to read, and incorporate a vast amount of information. For a reference book representative of British gynæcology it is felt that some minor improvements could be made.

The chapter on the reproductive cycle is not up to the standard of the rest of the book and could well be included with the chapter on the menstrual cycle and sex hormones to avoid overlapping. The illustrations of the endometrial cycle could be improved and further photomicrographs of ovarian histology would be an advantage, considering that many smaller student's textbooks include many such illustrations of a very high standard.

The chapter on puberty could well be omitted and normal puberty included with the menstrual cycle and menopause, and abnormal puberty absorbed into the excellent section on disorders of menstruation. Little guide is given to the practitioner on the management of distressing menopausal symptoms, and it is felt that some guide should be given about the hygiene of menstruation.

The treatment of genital tuberculosis throughout Britain at the present day is almost exclusively by anti-tuberculous drugs, supplemented in special circumstances by surgery, and treatment by X-ray has been, or should be, abandoned. Details of the irradiation techniques are given which seem unnecessary, as they do not represent current British gynæcological practice.

Considering the many new advances in the field of gynæcological endocrinology, it is disappointing to find that little indication of hormone values is given in both normal and pathological conditions, particularly functioning ovarian tumours and virilism.

A full account of the development of the genital tract is given and reference is made to the important recent work on nuclear sex differences, but the sections on the development of the urogenital sinus and external genitalia could be made clearer.

Apart from these minor criticisms, this book provides a very good account of present-day gynæcological practice, and the sections on disorders of menstruation and diseases of the cervix are among the best in the book.

It is to be hoped that subsequent editions will continue to improve and expand so that the book will take its place as the standard reference book on gynæcological practice in Britain.

W. G. M.

SURGERY OF THE SYMPATHETIC NERVOUS SYSTEM. By Professor Sir James Paterson Ross, K.C.V.O., LL.D., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S. Third Edition. (Pp. xii + 170; figs. 51. 35s.) London: Baillière, Tindall & Cox, 1958.

THE first edition of this book in 1933 was written at a time when the surgery of the sympathetic nervous system was in its infancy. A second edition followed four years later: perhaps too soon for a full evaluation of the results of operations.

The new edition gives a critical reassessment of the results of a long and wide experience in this field of surgery. This has necessitated rewriting many of the chapters so that a clear lead can be given to the surgeon, when and when not to operate.

The early chapters deal with the anatomy and physiology of the autonomic nervous system, including much recent work on both subjects. The second half describes the pathological processes leading to symptoms and signs in the peripheral vessels. Detailed methods of determining preoperatively the likely response to sympathectomy follow.

The text is written with remarkable clarity in simple English. This book is easy to read and contains a wealth of information. It should be carefully studied by all those who operate on the sympathetic nervous system.

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A HANDBOOK OF MEDICAL HYPNOSIS. By Gordon Ambrose, L.M.S.S.A., and George Newbold, M.B., B.S. Second Edition. (Pp. xiii + 276. 27s. 6d.) London: Baillière, Tindall & Cox, 1958.

BRAINWASHING and advertising techniques bear witness to the effectiveness of suggestibility. Hardly a day passes in the life of any practising medical man that he does not deliberately use it as part of his therapeutic approach. The effects of suggestibility must be taken into account in the design of any experiment to test the effects of a new drug. The 'inert tablet' has been found to be far from inert in many important respects. It is unfortunate therefore that more is not known regarding the mechanisms involved in hypnosis and suggestibility. Both are capable of scientific investigation, but little has been done in this field, mainly because of emotional attitudes engendered by their misuse in the past.

Ambrose & Newbold have produced a very readable book on the subject of medical hypnosis. The paucity of available scientific information on the phenomena of the hypnotic state, including E.E.G. findings, is all too obvious, but this has not deterred the authors from applying their methods to general medicine, psychiatry, anæsthesia, pædiatrics, dermatology, obstetrics, and gynæcology. Their case histories show how much they rely on the knowledge of the patients gained from a detailed psychiatric assessment of their history. In many instances they apply what can be regarded as a mirror image of the evolution of Freud's therapeutic approach—a short analysis followed by hypnosis when the dynamics of the problem are used for hypnotic suggestion. The same criticism applies to the results of hypnosis as to psychoanalysis in that, to be successful, the therapist must be a believer in the method. Individual case histories, the lack of controls, and the absence of independent assessment of results make it impossible to define any of the parameters in this field.

It is only fair to say that the authors are prudent in the midst of their enthusiasm. They exercise commendable caution in dealing with the problem of enuresis for example. They do not ignore the conventional medical approach where it is indicated.

A useful chapter is included on the techniques of induction.

This book is worthy of the attention of those who are at a loss to explain on purely physical grounds the therapeutic results they sometimes achieve. J. G. G.

A METHOD OF ANATOMY: DESCRIPTIVE AND DEDUCTIVE. By J. C. Boileau Grant, M.C., M.B., Ch.B., F.R.C.S.(Edin.). Sixth Edition. (Pp. xxv + 879; figs. 862; tables 23. 88s.) London: Baillière, Tindall & Cox Ltd., 1958.

AFTER a good *general* introduction, the book treats the topographical anatomy of the body *regionally*. The author, with a lifetime of teaching experience behind him, has written this book for the student, to be a companion during his dissecting-room studies, and a text for his revision work. Grant is always anxious to *explain* and to be *understood*. A vivid style; clear, simple diagrams; and a wealth of embryological, functional, and pathological correlation make him singularly successful in this.

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In the opening chapter a study is made of the mortality rate occurring from cancer of the urinary bladder in England and Wales, and a comparison of this mortality rate made with selected countries. That the disease is more common in workers in certain industries is well known, and a review of the disease from this aspect is made very fully by M. W. Goldblatt, J. G. S. Crabbe, and J. Watkins-Pitchford. Professor Boyland has contributed an excellent chapter on the disease from the biochemical aspect with an account of the experimental work performed on animals. There is a section on the pathology of bladder tumours by Cuthbert Dukes and R. C. B. Pugh. Their method of grading is used by most pathologists in this country and abroad with minor differences in classification. D. M. Wallace deals with the clinical assessment of the bladder tumour and describes the various sections of surgical treatment and, in addition, has combined with N. R. Mackay and D. W. Smithers to write an interesting chapter on the rôle of radiotherapy. Finally, there are sections on the complications of uretero-colic anastomosis, and a review of the various methods of treatment of bladder cancer.

This book is the most detailed study of cancer of the bladder that has yet appeared. It should be read by all surgeons engaged in the treatment of this disease and, in addition, the post-graduate student working for a higher examination will find much in it of great value. It is highly recommended.

J. McI. M.

MODERN TREATMENT YEARBOOK, 1959: A Yearbook of Diagnosis and Treatment for the General Practitioner. Edited by Sir Cecil Wakeley, Bt., K.B.E., C.B. (Pp. viii+312. 30s.) London: Baillière, Tindall & Cox, for the Medical Press, 1959.

THIS year Modern Treatment Yearbook has attained its semi-jubilee and is an established medical annual.

The past twenty-five years have seen radical changes in the theory and practice of medicine in all its branches. To acquire something of the new knowledge, to incorporate it with what he already knows, and to apply it in his daily work is not an easy matter for the busy practitioner.

The statistical surveys of multiple authorship which occupy so much of medical journals today make uninspiring reading at the end of a day's work. So the Yearbook fills a very definite need in presenting us with authoritative and readable articles on the many facets of modern medicine.

As examples of most helpful articles one may cite those on arterial hypertension, on carcinoma of the rectum and colon, on the management of cardiac infarction in the home and on liver failure.

In all respects the present volume maintains its previous high standard and can be recommended with confidence. W. G. F.

TREATMENT OF LUNG CAVITIES AND ENDOBRONCHIAL TUBERCULOSIS. By Beryl E. Barsby, M.D., M.R.C.P. (Pp. 147; figs. 46. 20s.) Edinburgh and London: E. & S. Livingstone Ltd., 1959.

THIS little book is an account of three years' study of the problems of the management of pulmonary tuberculosis in the State of Johore. It is essentially a thesis upon the importance of endobronchial tuberculosis, with special reference to the sociological and epidemiological conditions obtaining in Malaya. The author has bronchoscoped a very large proportion of early untreated cases and gives a full account of the bronchoscopic findings, and also the histology of mucosal biopsies. The relevance of these findings to treatment is emphasised. While many would disagree with some of the author's conclusions, especially as regard to treatment, one cannot fail to be impressed by the thoroughness of this study, and it should prove stimulating reading to those engaged in the field of tuberculosis. H. M. S.

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