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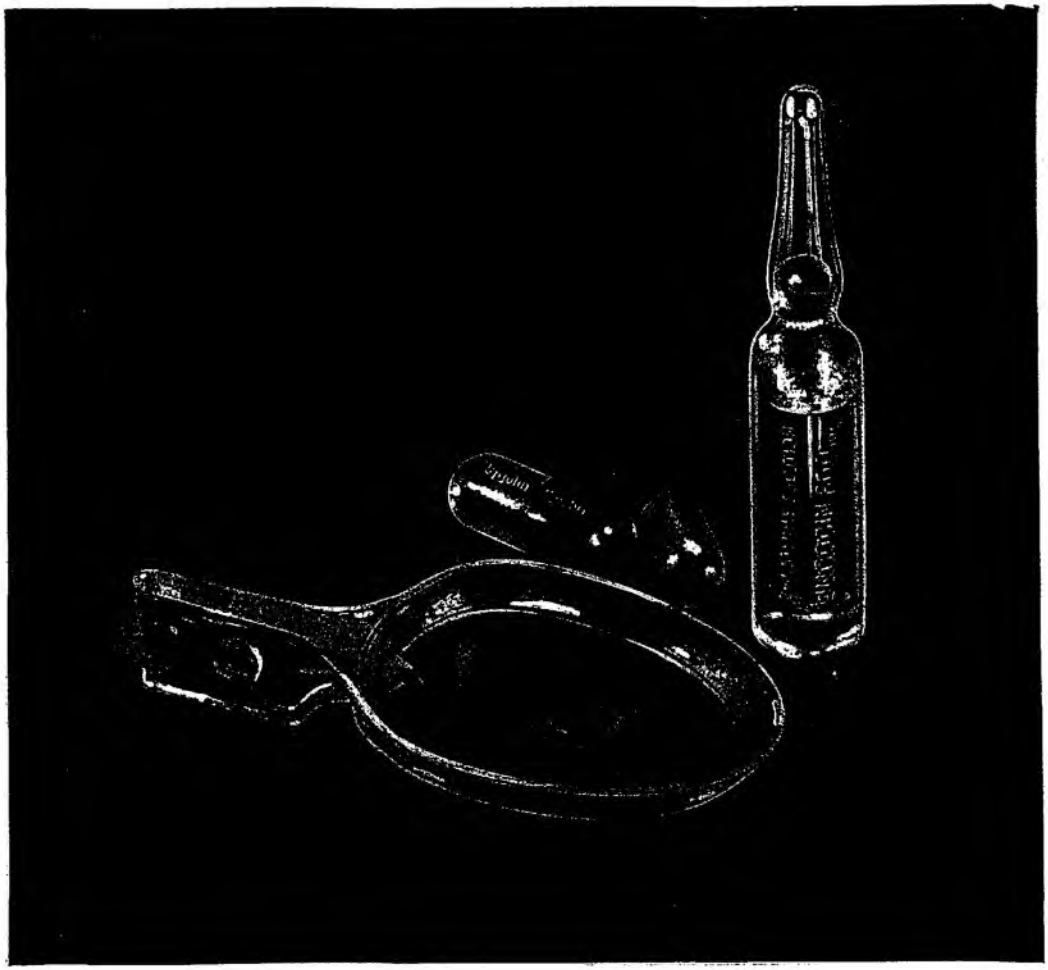

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VOL. VI. NO. 4. AUTUMN 1969

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Contents

EDITORIAL

The first part of the sale of most of the Royal Medical Society's Library at Sotheby's has been promising. The suggested upper limit of £120,000 is now attainable if the next two sales follow the pattern of the first. This is gratifying for the people who had to make the decision about the best way to dispose of the books.

It seems almost a paradox that the sale which was necessary for the Society to continue on a secure financial basis should, by realizing so much, have created a further dilemma. The problem can be simply stated as this: if the sale of the library produces a financial surplus over and above what is required for new premises and reasonable security for running those premises in the future, what is to be done with the surplus, or the interest from its investment?

Suggestions which have so far been put forward fall into two groups — those which improve the Society by improvement and extension of present facilities and those which can be seen as new ventures. Thus we have improvement of facilities and administration, aid to Res Medica, greater hospitality to visiting guests, more Society visits, bigger and better symposia and the foundation of an R.M.S. Scholarship Fund. All these are worthwhile in themselves and all have been suggested by different members at different times.

Perhaps the underlying problems need to be analysed before a decision is made. The whole question of the Society's relationship to the Medical Faculty comes into the decision.

Since the middle of the eighteenth century the books which are now being sold have been accumulating in the Society from various sources. Ostensibly they belong to "The Society" but in practical terms this means little. The number of medical students at any one time who take an active interest in the Society usually amounts to a couple of dozen, even though the membership is far greater than this. It would seem wrong for such a small number of students to be the sole beneficiaries and indeed no one would wish this to be so.

There are two paths which the Society can take and which it must be seen to choose between. It could remain a small group of people whose interest centres upon the Dissertation and discussion of medical topics. If it does this it must take it upon itself to adopt the role of medical promoter, meaning by this the organising of symposia, meetings and any other events with the whole of the Medical Faculty in mind and to which any member of the Faculty would be welcome. This is something like the pattern now emerging with Professor Barnard's visit, the Lauder Brunton Centenary Symposium and this year's Final Phase Forum coming to mind.

The alternative to this would be more radical and requires acceptance of the principle that the Royal Medical Society truly belongs to all medical students in Edinburgh. If this premise is accepted then the logical development from this would be the creation of a completely different kind of Society from the one that we have at the moment. Automatic membership or membership at a nominal subscription might remove the barrier that exists to people "just turning up". Recreational and comfortable work facilities would be an obligatory provision for all students rather than a bonus for joining, and if dissertation and discussion could be woven into this social framework a genuinely representative Society could be the outcome.

The decision about the sort of Society that Edinburgh is to have in the future is not one that can be taken by present members alone. It must be a decision by everyone in the Faculty and this can only be achieved by people "just turning up" to give their views.

MUTATION RESEARCH AND HUMAN WELFARE

Professor Charlotte AuerBach, F.R.S.

The Institute of Animal Genetics, Edinburgh.

From an address to the Society in November 1968

GENETICAL RADIATION DAMAGE

Knowledge gained from mutation research can be put to various uses for the benefit of mankind. One of them is assessment of genetical hazards from ionizing radiations. Before the war, this meant almost exclusively X-rays used in diagnosis and therapy. H. J. Muller, who in 1927 discovered the mutagenic action of X-rays, almost at once entered upon a campaign against the reckless use of radiation in medical practice. Especially in the USA, it was fashionable for the G.P. to have in his surgery a fluoroscope with, usually, an unknown and, often, a very high output of radiation and to use it indiscriminately even where less dangerous methods of diagnosis were available. There was also a practice of temporarily sterilizing men by radiation; when these men later on became fertile again they produced children from sperm that had been heavily irradiated as spermatogonia. In women, similarly high X-ray doses were used to produce fertility by follicle rupture. Until the war, the medical profession took very little notice of Muller. This careless attitude changed when fall-out and nuclear accidents became a major concern. Nowadays many national and international organisations, in all of which geneticists play an important role, are engaged in monitoring the amount of radiation to which we are exposed, in assessing its genetical consequences and in fixing "permissible" levels of radiation.

DOMINANT MUTATIONS

So much has been said and written about genetical risks from radiation that I can be brief. My main concern is to put them into perspective. They certainly should not be played down but they should also not be exaggerated. There is, for example, a widespread belief that children born to irradiated men or women are likely to be in some way abnormal. This is not borne out by observation nor is it expected on theoretical grounds. There are very few abnormal young among the progeny of heavily irradiated mice, and none were found among the children of Japanese parents that had survived exposure to the atom bombs. Theoretically, the type of mutation that would become manifest already in a child of the irradiated person would be a dominant mutation, and such mutations are known to be very rare. It is true that some Japanese women who had been pregnant at the time of the explosions had abnormal children, but these abnormalities were due to direct radiation effects on the foetus, not to effects on the germ cells of the parents. They do not constitute a risk for future generations for, like

the effects of thalidomide or German measles on the embryo, they are not inherited. If, as has been claimed, radiation of the embryo *in utero* increases the risk of infantile leukaemia, this too would not be a genetical damage.

CHROMOSOME BREAKAGE AND NON-DISJUNCTION

What, then, are the risks of radiation that causes so much worry to the geneticist? Chromosome breaks are one of them, although not the most important one. The reason is that chromosome breakage has serious consequences only when it results in a type of translocation that can be inherited and may result in the repeated births of children suffering from a "chromosome disease" like Down's syndrome. However, since a translocation requires the presence of two broken chromosomes in the same cell, it is not often produced by the low radiation doses from fall-out. Much greater is the risk that even these low doses will produce chromosomal disease through non-disjunction, and this has been taken into account in the most recent assessments of radiation hazards.

RECESSIVE MUTATIONS

The most serious radiation damage is due to recessive mutations, i.e. to mutations that become apparent only in homozygous individuals that have inherited the same mutated gene from both parents. Recessive mutations are not only the most frequent ones; they are also produced in direct proportion to the magnitude of the dose, so that there is no lower threshold below which they do not occur. Moreover, the vast majority of them are harmful or even lethal. This is not due to some special malice of Nature. It is simply a consequence of evolution which, in every organism, has selected an array of genes that act together harmoniously in development and that make the organism fit well into its environmental niche. New mutations are much more likely than not to disrupt this nicely adjusted interplay between the genes with each other and with environment. Although mankind certainly could be improved genetically, this cannot be achieved by radiation. For the non-geneticist, it is not easy to grasp the danger of recessive mutations for, by their very nature, these will remain hidden for several and, often, for many generations until affected individuals arise from the coming together of two gametes with the same mutated gene. Moreover, it will almost always be impossible to pinpoint a particular case of, say, phenylketonuria or recessive blindness as being due to a radiation-induced mutation, for radiation does not create new harmful genes, it only increases the frequency of the already known ones. Finally, not all recessive mutations have such drastic effects as blindness or idiocy. Many, probably the majority, are harmful only because they lower some component of fitness, e.g. resistance to infection or degree of intelligence. This can be concluded with a high degree of certainty from experiments on lower organisms, although it would be difficult to prove it for man. There can be little doubt that any increase in mutation frequency will eventually lead to an impairment of human health and happiness. It is our responsibility, especially that of the geneticists and politicians, to see that future generations will not have to pay too heavy a price for the security, health and comfort of the present one.

IRRADIATED FOODSTUFFS

Although it is not easy to arrive at good quantitative estimates of genetical radiation damage, there can be no doubt that such damage exists in all organisms and at all doses. The situation is quite different for another possible type of radiation damage which has recently become a subject of discussion. This is the possibility that foodstuffs may become mutagenic when they have been sterilized by the very high X-ray doses required for this purpose. Already seven years ago, Indian cytologists found chromosome breaks in the cells of plants that had been grown in heavily irradiated fruit juice, sugar solution or potato mash. More recently, the journal "Nature" created quite a stir among the circles concerned by publishing the results of an experiment in which a high frequency of mutations was found in Drosophila flies that had been reared on X-rayed medium. However, repetition of this experiment in many laboratories both here and abroad did not confirm these data: the results were either wholly negative or the increase in mutation frequency was only marginal. There the matter rests at the moment. The whole situation is typical for the uncertainties that beset attempts to generalize findings obtained with chemical mutagens; for it must be realized that, if heavily

irradiated medium should produce mutations, it would do so not through direct transfer of radiation energy but through the production of a chemical mutagen from one of the components of food. Whether such a chemical is formed will depend on the composition of the food; whether it will produce mutations will depend on the digestive and metabolic processes of the organism tested; even in the same organism, different cell types may respond in different ways to the same compound. All these considerations are of importance not only for the special case of irradiated nutrients but for the much more general question whether the exposure to mutagenic influences from chemicals used in industry, medicine, cosmetics, food additions, etc., is not at least as dangerous as the exposure to ionizing radiation from fall-out and X-rays. Indeed, this may well be true, but the uncertainties which I have just mentioned make it exceedingly difficult to arrive at conclusions.

GENETICAL DAMAGE FROM CHEMICALS

Caffeine is a case in question. The situation here is similar to that of irradiated medium. It has been known for a long time that caffeine produces mutations in microorganisms, and chromosome breaks and translocations in plants. It has been calculated that — if human germ cells show the same response — the amount of coffee consumed in the USA or of tea consumed in this country would give cause for serious concern. Experiments on animals, however, seemed to invalidate this conclusion. The results with Drosophila were similar to those obtained with irradiated medium : if there is an effect at all on Drosophila germ cells, it is exceedingly small. The question seemed important enough to test it in experiments on mice, which are much more laborious and expensive than those on Drosophila. Mice were given as much coffee in their drinking water as they could stand without ill effects; in some series, treatment was started already before birth by giving coffee to pregnant females and continuing the treatment on the progeny. Yet neither mutations not translocations were obtained, and for a time this seemed to settle the question. It was re-opened very recently by the finding that caffeine causes chromosome breaks in human cell cultures. It is true that these breaks do not seem to form translocations and therefore are not of the kind that is likely to have genetical consequences, but it is quite possible that this may be different in germ cells. On the other hand, it is also quite possible that no chromosome breaks at all are produced in germ cells. Again, the final conclusion remains doubtful, although the results with human cells certainly warn to caution.

It may seem overcautious to think that the chromosomes in two types of human cell might respond differently to the same mutagen. But this is just what has been found for formaldehyde. When formaldehyde is mixed with the food of Drosophila, it produces high frequencies of mutations in male larvae. Female larvae and adults of either sex are quite immune to its mutagenic action, although — as experiments with isotopically labelled formaldehyde have shown — it penetrates to their gonads. Even in the testes of male larvae, its action is restricted to one particular type of germ cell, the early spermatocyte. I have repeatedly been asked by pig breeders whether mutations may be produced by the practice of feeding breeding animals with skim milk that has been sterilized by formaldehyde. Now it so happens that, many years ago and for an entirely unrelated reason, I have shown that formaldehyde-treated skim milk powder is a good mutagen for Drosophila larvae. But how can one extrapolate from Drosophila germ cells to pig germ cells in the case of a mutagen that distinguishes between Drosophila spermatocytes and Drosophila spermatogonia?

It is this kind of consideration that makes it so very difficult to assess genetical hazards from chemicals. Yet the problem is so important that at present much money and effort is spent on arriving at some conclusions, however tentative. Among the substances for which evidence of genetical effects is being sought is LSD. So far the results have been contradictory : in some experiments, it has produced chromosome breaks in mammalian cells; in others, it has failed to do so.

CANCER THERAPY

There is one group of substances of such high penetration and general mutagenic action that their efficacy in producing mutations also in human germ cells can hardly be doubted. These are alkylating agents used in cancer therapy, e.g. nitrogen mustard. Almost certainly the probability of carrying a new mutation is higher among the progeny of

persons treated with such a compound than among the rest of the population. Since, however, the number of children to which this applies forms a negligibly small part of the whole population, this is not a serious genetical hazard for the population as a whole.

The use of alkylating agents in cancer therapy brings me to the positive applications of mutation research to human welfare. Elimination of cancer cells by chromosome breakage is one of them. It rests on the fact, mentioned before, that chromosome breakage kills only dividing cells and, therefore, acts specifically on malignant cells with their high dvision rate. All the same, it is usually not possible to exclude normal dividing cells, such as epithelial cells, from the irradiated area, and these too are likely to be killed by chromosome breaks. One of the aims of cancer therapy is, therefore, to increase the differential response of normal and malignant cells to radiation. Mutation experiments have given valuable suggestions on this problem. Substances have been found that act as sensitizers for chromosome breakage by radiation, while others act as protectors. If means can be found to introduce such substances selectively into malignant or normal cells, one might make the former more sensitive or the latter more resistant to killing by X-rays. The most powerful and generally effective adjuvant to X-ray effects is oxygen. A given dose of X-rays produces several times as many chromosome breaks in oxic as in anoxic cells. Moreover, only a fraction of the normal oxygen pressure is required to yield full sensitivity to X-rays, so that the sensitivity of normal cells is already at its maximum. Solid tumours, however, often have an anoxic core of highly resistant cells, and this may serve as a source of renewed malignant growth when the more peripheral and better oxygenated cells have been killed. This has led to attempts to improve the treament of solid tumours by radiating patients while they breathe oxygen or are infused intra-arterially with hydrogen peroxide. Neutrons are equally effective chromosome breakers in anoxic as in oxic cells; this is in part responsible for their efficiency in cancer treatment.

PEST CONTROL

Chromosome breakage is also made use of for a very different purpose, the control of noxious insects. You will remember that chromosome breaks or certain types of translocation kill zygotes into which they have been carried by one of the gametes. When males of Drosophila are exposed to very high X-ray doses, they remain able to mate and transmit sperm, but most or all of the eggs fertilized by the sperm fail to hatch. The idea therefore arose that the fertility of wild species might be drastically reduced by catching or rearing males, exposing them to high radiation doses and releasing them again into infected areas. This technique has already had a spectacular success in the case of the screw worm fly, which lays its eggs into the skin of cattle and used to be a great pest in the Southern States of the USA. Nowadays it has practically disappeared from these regions. Occasional invasions from Mexico, where no similar project has been carried out, are combated by the release of sterilized males from aeroplanes near the border. For other species, the technique may have to be modified in order to meet the special physiology or ecology of the insects. Thus in the boll weevil, a cotton pest, the dose of X-rays that kills males is only a little higher than that which sterilizes them, so that X-rays cannot be used for sterilization; chemical mutagens may give better results. For Tsetse flies, a project is now being worked out by which viable, heritable translocations — of the kind that in man causes Down's syndrome — will be introduced into wild populations. While this would not lead to an immediate and drastic reduction in hatchability, it should eventually become a self-maintaining device for producing heritable sterility. Insect control *via* chromosome breakage in spermatozoa is being studied in many countries and discussed at international levels.

IMPROVING THE GENOTYPE

Finally, let me mention the possibility of utilizing induced gene mutations for the benefit of mankind. In work with micro-organisms, this has already been done successfully. Fungi with a higher yield of antibiotics or yeasts with improved baking or brewing qualities can be produced with the aid of mutagens. However, in all these cases, the vast majority of mutations is not of the desired type and many are lethal or at least harmful to the organism. We have seen earlier why this must be so. In micro-organisms, of which huge numbers can be raised easily and cheaply, this wastage is no

impediment to the use of mutagens for improvement. Even in agricultural or ornamental plants, "mutation breeding" is being used quite extensively, especially in inbred strains whose genetic purity one does not wish to destroy by the introduction of desirable genes through crossing. In these cases, too, the loss of, perhaps, a thousand undesirable mutants for the sake of one desirable one may be worth while. For agricultural animals and, even more, for man improvement by induced mutation is out of the question unless treatments can be found which quite specifically produce certain types of mutation. The hope for this to happen is exceedingly slight, at least until the time when we can implant into embryos genes that have been extracted from selected donors or have even been tailor-made in the test-tube. Although this is a distinct possibility for the future, I do not think that it will materialize in mine or even in your lifetime.

DIAGNOSTIC PROBLEM

SET BY JOHN WALLWORK

SUBJECT

Female, age 51.

HISTORY

Pain for nine months of a sharp, gripping nature lasting a few seconds at a time and occurring several times per day. No relation to meals, etc.

ON EXAMINATION

A large mass in the right inguinal fossa was noticed by her General Practitioner on the evening of admission. Some tenderness and guarding was present. Patient was afebrile.

P.V.: Pelvis empty but lower pole of mass palpable high up on right side the mass having a soft consistency.

B.S.: Present.

PREVIOUS HISTORY

Duodenal Ulcer diagnosed several years earlier and treated medically with success.

Barium meal and follow through two weeks before admission showed no abnormality.

INVESTIGATION

Erect abdominal X-ray showed opaque area in right iliac fossa with a few scattered fluid levels in the large bowel.

A. What is the mass in the right iliac fossa?

B. What is the likely cause of the symptoms and signs described?

(Answer on Page 22)

OFFICE-BEARERS FOR THE 233rd SESSION

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" " Dinner Committee	Miss M. Y. MORRIS

THE PINEAL GLAND

Thomas Hamilton,
M.B., Ch.B., Ph.D., F.R.C.S.E.

Department of Clinical Surgery, Edinburgh University Medical School

Although the pineal gland (epiphysis cerebri) has been noted in medical writings for at least 2,000 years its possible physiological rôle remains unresolved. Early Greek anatomists, including Herophilus and his disciples, believed that the cerebral ventricles were the seat of the mind and that the pineal body or conarium had a sphincteric function to regulate the flow of thought. This concept was refuted by Galen who concluded that the pineal was probably a gland, similar to the lymph glands. Belief in a thought sphincter persisted and Galen ascribed this function to the cerebellar vermis.

In the seventeenth century Descartes established the idea that this organ was the seat of the soul. It is an awe-inspiring reflection of the power of Cartesian authority that, three centuries later, this is still the first association in the minds of many when the pineal gland is mentioned. His opinions were not accepted by everyone. Thomas Gibson, for example, in his descriptions of the anatomy of the brain in 1763 returned to the genital analogies of the early anatomists with respect to the pineal body.

"The first is *Glandula pinealis*, or Penis; because it representeth the Pine-nut, or a Man's Yard. It is seated in the beginning of that Pipe, by which the third and fourth Ventricles are united . . . This Gland des Cartes thinks to be the primary seat of the Soul, and that all animal operations draw their origine from it. But *Bartholin* has sufficiently confuted that opinion; for it seems to be but of the same use as other glands, and particularly the *Glandula pituitaria* placed near to it, viz. to separate the *Lympha* from the Arterial blood; which *Lympha* is resorbed by the Veins . . . Near to this on both sides of this third ventricle four round bodies appear. The two upper are lesser and are called *Testes*: the two greater are lower, and are called *Nates*. The chink between the *Nates* is called *Anus*".

In the twentieth century these philosophic postulates of sphincter of the mind and repository of the soul have been supplanted by ascribing a neuro-endocrine function to the pineal. Initially this idea developed from the observation of clinical relationships. In 1898 Heubner reported that a boy who had been observed to have precocious somatic and sexual development died with a tumour of the pineal gland. Associated changes in sexual development have been noted in about one third of case reports. Sexual precocity is a particular feature of pineal tumours in boys. It is a matter for debate whether the effects upon the gonads result from disturbance of pineal endocrine activity, from associated pituitary dysfunction or from the effects of pressure upon the hypothalmus. Kitay and Altschule in their review of the literature up to 1954, concluded that precocious puberty resulted from reduced pineal activity, whereas true pineal tumours with increased activity caused delayed sexual development in children.

Such observations from the field of clinical medicine have naturally led to a renewal of interest in the pineal body from time to time and investigations have been extended to the experimental laboratory. A number of these studies indicate that the pineal gland and its secretions may have an important rôle in the modification of endocrine function by environmental influences.

ment cells. Subsequent chemical analysis identified the active principle as N-acetyl-5-methoxytryptamine or melatonin. Within the next few years Bagnara had conducted some elegant experiments on tadpole melanocytes. He concluded that melatonin (or a similar amine) was secreted by the pineal in response to darkness and that, in conjunction with pituitary melanocyte-stimulating-hormone (MSH),

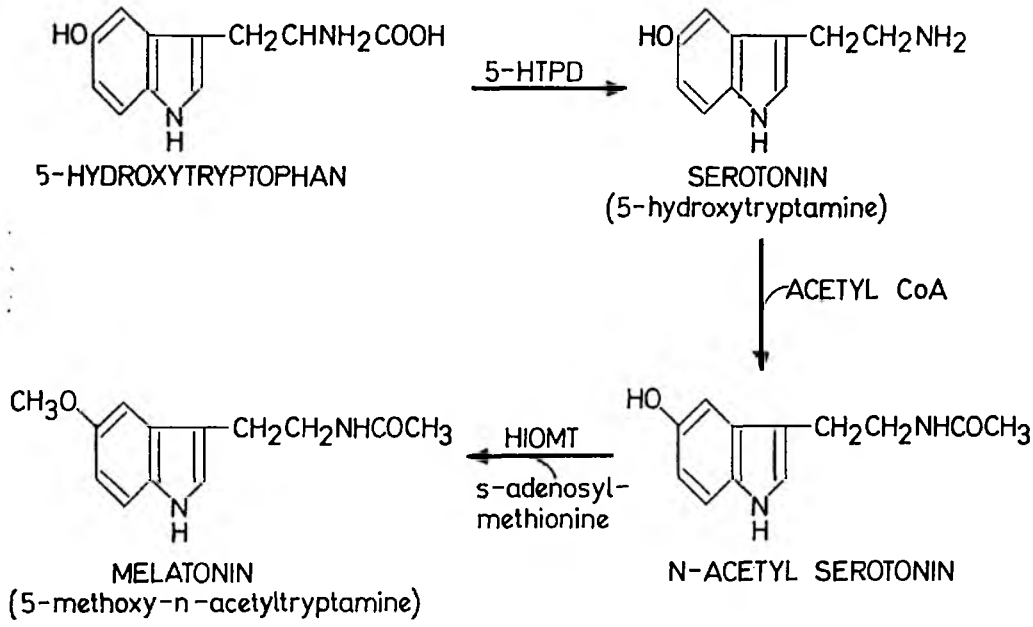

FIGURE 1

Metabolism of 5-hydroxytryptophan to melatonin in rat pineal gland as suggested by Wurtman. The enzymes 5-HTPD (5-hydroxytryptophan decarboxylase) and HIOMT (hydroxyindole-O-methyl transferase) are under photoperiodic control, the activity of the former increasing during illumination and of the latter during the hours of darkness.

PINEAL HORMONE

A significant contribution to knowledge of pineal function was made by Lerner and his colleagues in 1958. From bovine pineal glands they extracted a substance with the remarkable property of blanching frog's skin. This is the most powerful agent known to cause aggregation of melanin granules in amphibian pig-

it was concerned with the adaptive responses to changes in environmental illumination.

The biosynthetic pathways from tryptophan to melatonin have been established by Axelrod and his collaborators (Fig. 1). The essential final step from N-acetylserotonin is effected by the enzyme hydroxy-indole-O-methyl-transferase (HIOMT) with co-factor S-adenosyl-methionine as a methyl donor. This

enzyme and the capacity to synthesize melatonin has been restricted to the pineal glands of all mammalian organs so far investigated. Relatively small amounts of melatonin can, however, be manufactured by the brain and eye of some birds and amphibia.

The stage was now set for the collation of these findings with earlier and concurrent observations on the biological effects of excision of the pineal gland, administration of pineal extracts and the suppression of pineal "activity" by manipulation of the environment.

EFFECTS OF LIGHT ON THE PINEAL GLAND

The most striking effect of exposure to continuous illumination in rats, the species most frequently studied, is the induction of a state of persistent oestrus in females. In association with this there is a marked decrease in the size and weight of the pineal gland. Melatonin content and HIOMT activity are depressed.

Quay has found that serotonin levels in the pineal are greatest at mid-day and lower at night. In contrast melatonin content is low by day with peaks after darkness.

ANATOMY OF THE PINEAL

The Dutch neuro-anatomist Ariëns Kappers has made a particular study of the anatomy of the pineal gland. Although the epiphysis is embryologically of diencephalic origin it loses all nerve connections with the brain soon after birth. The pineal gland of the adult is richly served by sympathetic fibres deriving their origin from the superior cervical ganglion in the neck and entering the skull in association with cerebral blood vessels. Electron-microscopic studies have revealed sympathetic nerve endings terminating directly on pineal parenchymal cells.

During its evolutionary development the pineal has become modified from the light-sensitive structure of amphibia — the "third eye" — to an organ in which the morphological characteristics of its cellular elements are more suggestive of a glandular, secretory nature. Recent studies have confirmed the opinion expressed by P. T. Herring of St. Andrews in his monograph of 1927 that "the mammalian pineal body cannot be regarded morphologically or histologically as a vestigial structure. It is not a remnant of the parietal eye of reptiles, but an organ which persists throughout the vertebrate series and attains a high degree of specialisation in higher members of the series".

THE PINEAL AND THE GONADS

The effects upon the gonads of excision of the pineal gland are similar to those resulting from exposure to continuous light. These include hypertrophy of the gonads, acceleration of vaginal opening and prolongation of oestrus. It has been shown further that these effects can be reversed or blocked by the administration of pineal extracts or melatonin. The fact that the changes induced by light or by excision of the pineal are not additive is suggestive of the gland being concerned in the mechanism of light-induced alterations of gonadal function.

By the use of suitable radioactive tracers melatonin is found to be concentrated not only in ovaries but also in the pituitary. Further evidence that the pituitary is involved in the pineo-gonadal relationship is derived from the observation that pinealectomy increases pituitary gonadotrophins but the administration of pineal extract reduces the gonadotrophin content of the pituitary and the level of circulating gonadotrophins.

The nervous pathways integrating retina, superior cervical ganglion and the pineal gland have not been established. Their existence is indicated by the blockage of light-induced changes in the gonads which results from both enucleation of the eyes and bilateral superior cervical ganglionectomy.

From these and other observations a plausible theory of possible pineal function has been put forward by Wurtman, Axelrod and their colleagues. The pineal gland seems to operate as a "biological clock" by converting into hormonal terms the cyclical nervous activity induced by changes in environmental lighting thus influencing target organs of which the gonads are pre-eminent.

THE PINEAL AND OTHER ENDOCRINE ORGANS

A relationship to other endocrine organs has not been so clearly established. There are suggestions that the thyroid gland is affected by excision of the pineal; and that, conversely, suppression of thyroid function results in alter-

ations in pineal constituents. The evidence is so far inconclusive.

The pineal gland does seem to influence the adrenal glands. Attention has focussed mainly on aldosterone production. Although conflicting results have been obtained most studies indicate that the pineal, and extracts from it, stimulate aldosterone secretion.

ENDOCRINE RHYTHMS

In 1943 Pincus demonstrated that an increase in urinary ketosteroid excretion occurred in the evening. Since that time a variety of endocrine products and their physiological consequences have been shown to fluctuate in an approximately 24-hour or circadian rhythm. These include the secretion of corticosteroids, the number of circulating eosinophils, ascorbic acid levels in the ovary, prolactin content of the pituitary, the level of thyroid-stimulating hormone in the blood and many others. Such rhythms have been observed in several species from birds to man and some can be influenced by suitable manipulation of environmental lighting. Many of these phenomena, however, revert to what appears to be intrinsic rhythmic activity after an initial response to environmental changes. Others appear to depend more directly upon environmental lighting for their cyclical behaviour and it has been suggested that even endogenous rhythms may be governed by natural illumination acting as a "Zeitgeber". The possibility that the circadian rhythm of pineal amines is concerned in this mechanism awaits confirmation.

In many species photoperiodic influences govern seasonal behaviour which is under endocrine control. For example, many birds respond to the "long days" of spring by sexual maturation. Dutch and Japanese farmers have traditionally exposed song-birds to extra illumination in the autumn to induce singing in the winter — a phenomenon dependent upon testicular function. Other species, like the sheep, come into oestrus during the "short days" of autumn in the northern hemisphere, and the timing of oestrus can be set by suitable alteration of environmental illumination.

The complex nature of these behavioural phenomena is demonstrated by the ferret. Premature oestrus can be induced by the addition of an extra hour of lighting at midnight in winter or by increase in the artificial day-length to 14 hours. However, the totally unnatural schedule of 2 hours light, 10 hours darkness. 2 hours light, 10 hours darkness in the day achieves the same effect.

That man is not spared from such influences is indicated by Zacharias and Wurtman who found that the onset of the menarche occurs more than a year earlier than in normal adolescents in those girls blinded at birth by retrolental fibroplasia. It is also of interest that the phenomenon of "furore sexualis" in the Esquimaux after the long winter days may be an example of man's seasonal behaviour in response to environmental factors.

THE PINEAL GLAND AND MALIGNANT TUMOURS

In the Department of Clinical Surgery we have found that the induction of either simple or malignant mammary tumours in the rat by carcinogenic hydrocarbons can be modified by environmental illumination. Exposure to continuous light results in predominantly fibroadenomatous tumours. There are associated changes in the pituitary, ovaries and pineal gland. The administration of melatonin has resulted in a significant increase in the number of mammary adenocarcinomas induced by the carcinogen.

An interesting association between the pineal gland and cancer in man has been reported by Rodin and Overall. In their autopsy series the size and weight of the pineal was significantly increased in patients who had died from a variety of malignant diseases compared with those in whom death was caused by non-malignant conditions. The pineal gland was shown to be enlarged in the middle-aged and elderly. This is not, as might be anticipated, solely the result of increasing calcification. Functional parenchymal tissue remains and enzymic activity is high even in the elderly. There is obviously a need for more careful study of the pineal gland which is rarely considered during routine post-mortem examination.

CONCLUSION

For centuries the pineal gland has been one of the enigmas of the central nervous system. The evidence from recent investigations suggest a physiological rôle as a neuro-endocrine transducer by which environmental information modifies the function of the gonads and related endocrine organs. Its main clinical value remains as a useful landmark in neuroradiology but it can no longer be regarded as a functionless vestigium.

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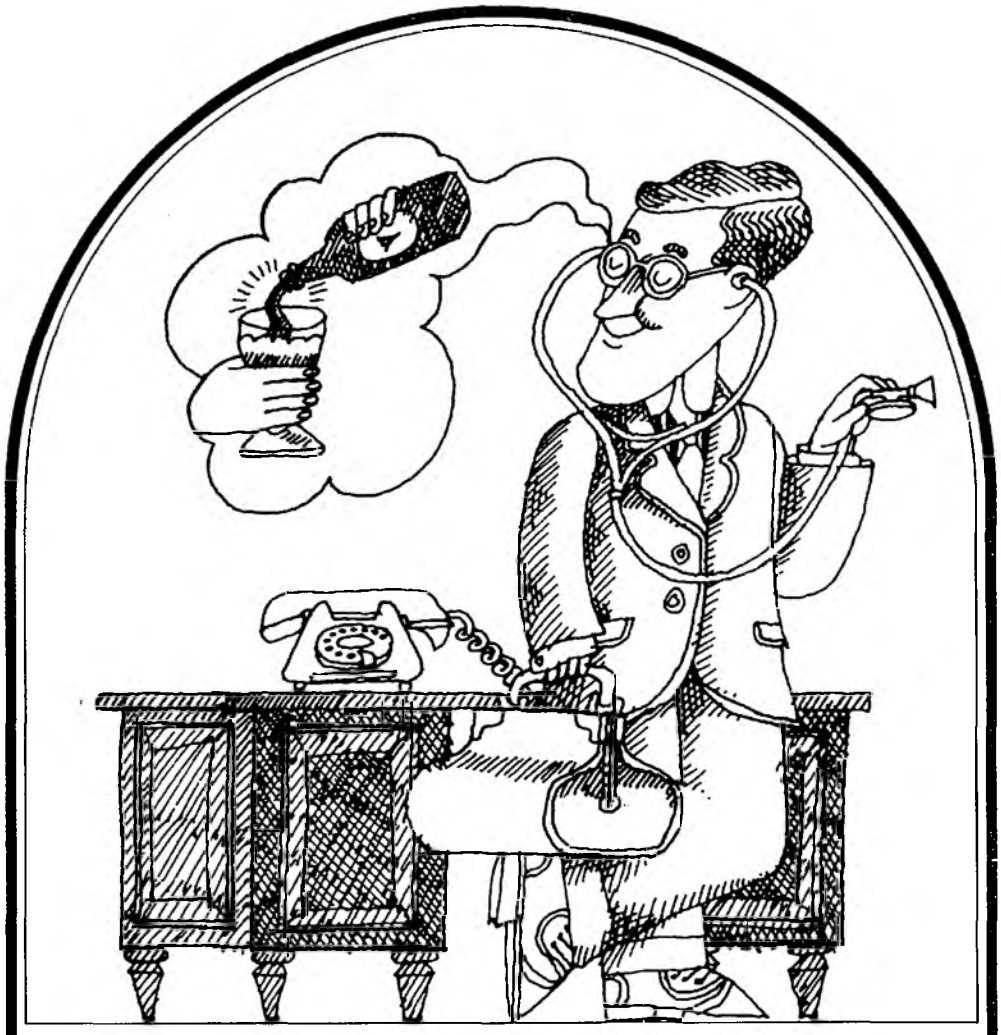

Q. *What do medical men require ?*

A. *Medical men require syringes, cheerfulness, couches, devotedness, telephones, watchfulness, sleep, firmness, knowledge, gentleness, stethoscopes, alertness, telephones, readiness, patience, kindness, sleep, promptness, diagnostics, rightness, telephones, awareness, telephones, long-sufferingness, sphygmomanometers, acuteness, secretaries, calmness, telephones, soothingness, sleep and goodness and* **GUINNESS**

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THE CHLOROFORM CONTROVERSIES

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It was the introduction of ether by Morton in 1846 that provided the necessary conditions for the development of Modern Surgical practice. Previous to its use Surgery was swift and brutal, its scope confined to the body surface, i.e. the evacuation of pus, amputation of limbs, excision of superficial tumours. It is revealing to examine the operations performed in the Royal Infirmary, Edinburgh, in the years 1831-34, a total of one hundred and forty, an average of thirty-five a year. Hovell remarks, "Although in 1829 the staff of the Royal Infirmary included surgeons of great reputation, very few operations were performed, and the operation theatre served little purpose."

It is hard today to realise the impact of the new discovery on the medical profession, yet in a very short time ether was to be supplanted by chloroform. I have often wondered why this happened. History is rather vague on this point. The major objection appears to have been its unpleasant smell. I suspect there were other reasons. The entrepreneurs of the time, realising the importance of the event, were anxious to participate in it. A frantic search for new drugs began and in November 1847 Simpson of Edinburgh used chloroform, first in obstetrics and then nearly six months later in general surgery.

In retrospect one feels it was unfortunate that this potent drug was discovered and used so soon after the introduction of ether, as most doctors of the period were ill-equipped to handle it. Almost from the time of its inception, chloroform was beset with controversy, often bitter, frequently uninformed, always unsavoury. Dissension arose as to who deserved the credit for its 'discovery'. It was prepared by Souberain in France and Guthrie in America, used as an anaesthetic by Heyfelder and Flourens but in animals, Jacob Bell and William Lawrence of London had tried it out in a weak mixture with alcohol and abandoned it. Waldie, a Liverpool chemist, had suggested its use to Simpson, who acted on the suggestion. How does one distribute the honours? Simpson had the courage to use it in clinical practice and the energy to publish his results before anyone could beat him to it. On these grounds he deserved the credit. Perhaps he could have been more generous in his acknowledgements, but it was not a generous age.

With the introduction of chloroform, the use of ether rapidly declined, and it is hardly surprising that within two months the first death under chloroform was reported. On January 28th, 1848, Hannah Greene, a fit young woman aged 15, died two minutes after the induction of anaesthesia. Other reports of a similar nature soon followed. The 'unexplained' death of healthy young adults caused considerable anxiety in the profession, particularly in England and America. In Scotland up to this time no death had been reported. Briefly, the following situation developed. The

Medical profession in England and America postulated that chloroform acted primarily on the heart muscle, producing acute Cardiac Syncope. This occurred irrespective of dose and concentration, and the Cardiac Syncope occurred before the cessation of breathing. Simpson and his supporters, later known as the Edinburgh School, claimed they had not experienced a single death from its use. Primary Cardiac Syncope did not occur: death was always secondary to severe respiratory depression, i.e. to overdosage. They taught, "Watch the respiration and the circulation will look after itself." They believed that death was avoidable and unnecessary and said so in no uncertain terms.

By 1858 fifty deaths had been reported in England and America, and there is reason to believe that many more had been concealed. The Edinburgh School claimed no deaths, although there is evidence now available that one patient died in 1853. In this they were supported by John Snow, probably the first professional anaesthetist (an Englishman), who reported a series of four thousand cases without trouble. Snow carried out a series of experiments on dogs, using a measured concentration of less than 4% chloroform diluted in air. He observed that first the respiration was depressed, then abolished. The heart continued to beat forcibly. If the anaesthetic was withdrawn and artifical ventilation was instituted the animals recovered; if not, the heart failed. He concluded that Cardiac Syncope was secondary to respiratory failure. If the dosage and concentration were carefully controlled there was no danger. He developed a dosimetric method for the administration of the drug and his results were unsurpassed. However, in the years following, reports of sudden death under chloroform continued, and by 1864 they numbered 124. The positions of the two sides were deeply entrenched, and the Royal Medical and Chirurgical Society (now the R.S.M.) set up a committee to examine the problem. They concluded that inhalation of a mixture of 2-4% chloroform in air was safe. If these concentrations were exceeded the risk of Cardiac and Respiratory depression increased. In effect the published report of this committee led to the abandonment of chloroform in England. Scotland, however, continued to use it, and it was not surprising when, at the 43rd Annual General Meeting of the British Medical Association in Edinburgh in 1875 the Section of Surgery passed a resolution "that it is desirable a committee be appointed to enquire and report on the use of chloroform." This committee was an extraordinary one. It consisted of fifteen members, many of them distinguished. They hailed from the four corners of the British Isles — Aberdeen, Edinburgh, Dublin, London. It is not surprising that it did not meet till 1877, when Spenser Wells the chairman suggested that the Scientific Grants Committee should engage a competent investigator to do the work. This, however, was refused, and a sub-committee, all of whose members belonged to Glasgow, was appointed. The Glasgow Committee report concluded that chloroform was more dangerous than ether. Their findings delighted the English, incensed Edinburgh and achieved little change. The etherists were happy, the chloroformists unimpressed.

In the years following the Glasgow report, ether was becoming the anaesthetic of choice. Then in 1889 an extraordinary situation arose. Surgeon Major Lawrie, Principal of the Hyderabad Medical School, announced at the annual prizegiving day his experiments with chloroform. He claimed 128 dogs had been given chloroform till they died, and in no case was the heart affected until the respiration had ceased. In the Medical School many thousands of chloroform anaesthetics had been administered without a single death. He added a few appropriate(!) remarks about London and Glasgow and their committees.

The Lancet challenged Lawrie in an Editorial, but he replied "I hold there is no such thing as chloroform syncope". He offered £1000 to the Lancet if they would send a representative to repeat the Hyderabad experiments. The Lancet accepted the offer, and appointed Lauder Brunton, F.R.S., a distinguished pharmacologist, to undertake the investigation. The results reported by Brunton (known as the 2nd Hyderabad Commission) confirmed Lawrie's findings in every respect.

The Lancet, under some pressure from the profession, remained obdurate and took the line that animal experiments were not acceptable. It was unfortunate that Lawrie used unscrupulous methods in an attempt to advance this case for chloroform and eventually the Lancet, the academics and the Medical Profession declined to regard his claims as serious, although the experimental evidence was not challenged.

The controversy went on. At this period many distinguished Physiologists, Gaskell and Shaw, Leonard Hill and McWilliam, Sherrington and Walker became interested in the problem, and although the by-products of their work, cross circulation technique, Wallerian degeneration of nerves, were important, the problem remained confused. Briefly, the work of the physiologists confirmed the belief that chloroform acted on the heart, but only during deep anaesthesia when very high concentrations were used. This was in direct conflict with the clinicians who insisted that death occurred during light anaesthesia (during induction) when the concentration of drug was low. It was not till 1911 that Levy appeared to provide the answer. He administered chloroform to cats receiving an infusion of adrenalin. Many of these animals developed ventricular fibrillation and sudden death. He concluded that chloroform per se did not cause Cardiac Syncope, an exciting cause had to be superadded. He cited as such causes, the release of adrenalin, inhibition or stimulation of the vagus, anoxia and strong sensory stimuli. It should be clearly understood that he *did not* perform experiments to prove this. One is inclined to ask why indigenous adrenalin in the frightened cat was not enough to produce sudden death. However this explanation matched the clinicians' concept of sudden death in light anaesthesia, and the use of chloroform was largely discontinued.

At about this period a second objection to the use of chloroform was raised, i.e. its effect on the liver. Cases of acute hepatic necrosis following its use began to appear in the Journals, and 'Delayed chloroform poisoning' became a clinical entity. It is interesting to speculate why fifty years elapsed before reports of its effect on the liver appeared in the English Journals. One possibility is the rapid advances being made in Surgery. Surgeons were beginning to explore the abdominal cavity: these operations were longer, required muscle relaxation and hence the dose and concentration of chloroform used would be much higher.

A review of the literature from 1900-1925 in an attempt to assess the incidence, and the factors responsible for causing liver damage in man, was unsatisfactory. Many are reports of isolated cases. Even the pathological criteria of acute hepatic necrosis varied, from evidence of 'fatty degeneration' to the classical picture of acute cellular destruction. Data from the pre-operative state of the patient is vague, time of operation, dosage and concentration of drug used were rarely mentioned and the only conclusion possible was that acute hepatic necrosis was a rare complication of patients undergoing Surgery and chloroform anaesthesia. Its incidence seemed to be more frequent in three groups of patients: the very young, the toxic, and women suffering from the toxaemia of pregnancy.

The experimental work in animals was much more conclusive. Stiles showed that under his experimental conditions chloroform could produce acute liver damage. However, it must be stressed that these experiments were designed to destroy the animal. The animals received choloroform day after day for many hours — the dosage, although not recorded, must have been immense — until they died and autopsy revealed acute liver damage. Autopsy also revealed serious bronchopneumonia and severe renal damage. In these experiments chloroform was not used as an anaesthetic agent.

However, the fear of cardiac and hepatic failure banished chloroform from anaesthetic practice, although it must be admitted that a few sturdy chloroformists ignored the evidence, which was contrary to their experience, and continued to use the drug, in some instances surreptitiously.

The introduction of Halothane, an halogenated hydrocarbon with many properties similar to chloroform, in 1956, led us to attempt a reassessment of chloroform. This had been done by Waters in 1951, but it was felt that it should be used in the context of Modern Anaesthesia, i.e. where the anaesthetic agent provides sleep, analgesia and areflexia, but not muscle relaxation.

HEPATOTOXIC EFFECTS

These were studied in thirty-eight patients, half receiving Halothane and half chloroform. The transaminase tests were used to assess acute hepatic damage. These tests were carried out pre-operatively, 24 hours post-operatively, and on the third day after operation. There was no significant difference in the two groups of patients, and there was no evidence that either of these agents produced liver damage. Furthermore, in a ten-year period 1958-68 many thousands of patients

have received chloroform and no clinical evidence of Acute Hepatic Necrosis has ever been recorded.

CARDIOVASCULAR EFFECTS

In analgesic doses, pulse and blood pressure are normal. Contrary to some teaching, arrythmias do not occur. With deeper planes of anaesthesia the pulse slows and the blood pressure gradually declines. With gross overdosage the heart would cease in asystole. Even in deep anaesthesia, provided ventilation is adequate arrythmias are very rare.

CONCLUSION

In the last ten years chloroform has been used extensively to provide sleep, analgesia and areflexia, but not muscle relaxation. In this context no serious cardiovascular or hepatotoxic effects have been noted. It is a potent drug, its effects being similar to that of Halothane, it has the advantage of being very much cheaper. In retrospect the Edinburgh School were right, but the profession as a whole were not ready for its use. The ensuing misuse of chloroform, led to it being abandoned.

ANSWERS TO DIAGNOSTIC PROBLEM

(See page 12)

A. Distended colon.

B. Carcinoma of the hepatic flexure of the colon.

ASSESSMENT OF THE PSYCHOLOGICAL STATE

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THE MENTAL STATE

Numerous of the clinical signs characterizing the mental state of the patient will have become apparent during history taking. The clinician then has the opportunity to study any aspect of the psychological state which calls for special further evaluation.

1. *General appearance and behaviour:* The patient is described tersely but vividly, to provide a record which will suffice to call him to mind as he looked when in the examination room: his posture, his expression, his clothes, his mannerisms, his reactions to the clinician, and his mode of presenting himself. In the case of a mute or stuperose patient this aspect of the mental state may be among the most revealing.

2. *Thought processes:* Talk is externalized thought, thus the clinician notes how ideas are handled and the manner in which the patient arranges and expresses his concepts. The major pathology may be in this psychological sector, and be disclosed in disordered syntax: as when a schizophrenic patient juxtaposes apparently unrelated references to a portion of his body and the river he lived close to as a child: "This is my arm and the Couch is in Essex".

3. *Sample of Talk:* A segment of conversation is written down, in the patient's own words, to convey in precise context his major preoccupations.

4. *Mood:* The clinician has already obtained much evidence about the prevailing affect before he asks the patient, "How do you feel in yourself?" or "What is your mood like?" The patient may then state in dispirited tones that nothing that takes place means anything any more — "it's all flat". In some instances sadness is not mentioned directly; instead the patient talks of a dead sensation in his chest or a heaviness in his head, or the deeply pessimistic patient describes the surrounding world as grim and hopeless.

5 *Delusions:* The patient may disclose that he has developed false beliefs, misinterpreting everyday events as specially significant or attributing unwarranted intentions to people with whom he comes into contact. They are seen as intensely concerned with him, pestering him or maligning him or scorning him. He may not arraign particular people. "I know from the way I've been feeling that there is some evil force that is directed onto me by supernatural powers".

6. *Hallucinations:* When a patient perceives

sensations — visual, auditory, tactile, and so on — in the absence of any actual external stimulus, he may readily tell the examiner about them, or he may conceal the mental experiences which he himself has found startling.

"During the morning of the 10th of March, I was de-frosting my refrigerator when I distinctly heard my husband in his office, which is completely away from our house in an entirely different street. I heard him having consultations with three different people, then dictating letters and talking to his secretary. It seemed to me that I was actually hearing what was happening at that precise moment. I became rather alarmed when by lunch time the voices of all the members of my family were distinctly audible and almost incessantly present. During the early afternoon I was most disturbed to hear a strange male voice which was loud and clear. I got absolutely no peace from this voice which was accompanied by music, and a mixed choir which had the quality of what I would call Church music. After the evening meal was over this became so loud and persistent that I felt anyone in the room with me could not fail to hear it. Therefore I escaped by myself on every possible occasion: my husband became very curious about the reasons for my frequent disappearances, and in the end, I took him into my confidence."

7. *Obsessions*: These are thoughts — ideas or images — which the patient regards as foreign and tries to dispel, but which nevertheless persist:

"The idea keeps coming back that I may be pregnant. I can't be quite certain. I've never had intercourse, and my periods never stopped, so with my logical mind I know it's impossible. I think over and over again that I may be having a child. I've sent away to an agency for a pregnancy test, and I saved up for an abortion."

Compulsions are repetitive actions, the counterpart of obsessions in overt behaviour.

Abnormalities are found in the remaining psychological sectors when there is either acute or chronic brain impairment, leading respectively to temporary or permanent intellectual defect.

8. *Orientation*: An estimation of the patient's capacity to orient himself in time and space emerges as the history is taken, and more accurate assessment is gained by testing the patient. The following five questions can be used as a test, a score of 1 point given for each correct answer:

1. What year is this?
2. What month is this?
3. What day of the month is this?
4. What is the place you are in now?
5. In what town is it?

9. *Memory* is tested by assessing the patient's ability to recall remote and specially recent events. The clinician may already have noted gaps or inconsistencies in the patient's account of himself. An unimaginative but effective question is to ask what he had for breakfast.

10. *Attention and Concentration* are attributes of a normal person whose sensorium is lucid. In delirium, for example, normal alertness and attentiveness are lacking. The patient cannot calculate an arithmetical sum correctly: asking him to subtract seven from 100 is a classical test.

11. *General information* is tested by asking the patient questions such as the following: Who is on the throne? Who ruled before? Who is the Prime Minister?

12. *Intelligence* is assessed from the detail and subtlety of the patient's account of himself, his capacity to reason, and the extent of his knowledge. Accurate measurement is made by use of standardized intelligence tests.

13. *Insight and Judgement* is the final sector in the examination, and deals with the extent of the patient's recognition that he is ill, his grasp of the nature of the disorder, and the realism of his judgement about his future.

DIAGNOSING THE PERSONALITY

The personality may be defined as the sum total of a person's actions and reactions. Abnormalities of personality are expressed particularly in the individual's relationships with other people. Personal relationships are differ-

ent from usual — in specific ways — when the personality is disordered.

The clinician diagnoses the personality by two clinical techniques. The first is applied during the history-taking. At the same time as he gathers the facts about the illness, he listens to gather the characteristic and repetitive behaviours which the patient describes, e.g. A man may give repeated instances of gross and passive dependence, first on his mother and later on a teacher, an employer, his wife, etc. The clinician registers mentally, as he notes down these specimens of the patient's social responses, that a morbid pattern of passivity and clinging appears to be emerging.

The second procedure depends on the use by the clinician of his own personality as an instrument in the clinical interaction. The clinician knows — or should know unless inadequately trained in interviewing — what effect he has on people, i.e. what behaviour he evokes from them. The knows from experience which reactions to him are exceptional, as when a patient becomes unduly aggressive, or tends to be aloof and detached, etc. If now the passive patient mentioned above begins to stimulate the clinician into feeling that excessive demands are being made of him, that the patient will become a burden on him, a dead weight, the tentative personality diagnosis suggested by the patient's own account will have been supported, and the mode of relating characterized which impairs the patient's adjustment. The doctor has observed his own responses to the patient, and used these as clinical information. The patient may have asked for special tonics, may indulge in special pleading for another appointment in the very near future, may comment on the extent of his reliance on the doctor to take good care of him, etc.

A third possible step to confirm these two sources of clinical information about the personality structure is to request formal personality testing, to be carried out by a clinical psychologist colleague.

THE DIAGNOSTIC FORMULATION

The fourth part of the psychiatric examination is a technical decision-making procedure. The doctor co-ordinates all the data he has derived from the patient, decides on the relative weighting he will give to the different elements in the case, and arrives at a diagnosis. In psychiatry this consists of two parts :

(i) The naming of the disorder (or *nosological diagnosis*): the term to be applied to the illness depends on the most prominent symptoms and signs in the case, constituting one of the syndromes or disease patterns which can be found described in standard psychiatric texts. e.g. Depressed mood, suicidal impulses, loss of appetite, retardation of thinking, physical apathy, self-reproach and insomnia point to endogenous depressive psychosis.

(ii) *The psychodynamic formulation* : the second part of a psychiatric diagnosis lists, in a coherent sequence, the pattern of factors which the clinician considers to have contributed to bring about the illness, e.g. "The patient, the submissive member of an identical twin pair, is less attractive than her sister; during childhood her mother discriminated against her, and the patient is now resentful and hostile. She tried to suppress these impulses in order to win affection from those to whom she forms over-dependent attachments (e.g. twin sister, husband). Her illness began when she found evidence in her husband's wallet that he was associating with another woman."

Because in successive examinations the patient may communicate fresh biographical material, the psychodynamic formulation becomes gradually fuller as confirmation is obtained for particular dynamic factors in the patient's adaptive pattern. (The nosological diagnosis may also in some cases have to be revised.) The formulation of the illness can well be tested — in many cases — by communicating it to the patient (in words he can grasp), and the patient himself can then inform the clinician how aptly he is succeeding in grasping the manifest and the latent clinical facts in the patient's case.

The first part of this article appeared in the last edition of Res Medica.

GROWTH HORMONE AND THE LIPOLYSIS OF EXERCISE

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From a dissertation read before the Society on January 22nd, 1969

Growth hormone (GH) is secreted by the acidophil cells of the anterior pituitary. It is a protein, partially α-helix in strucure, of molecular weight 29,000 in man(1). In addition to its effect in promoting growth several metabolic effects follow its administration, one of which, the mobilisation of free fatty acid (FFA) from adipose tissue, will be discussed in some detail.

The radio-immunoassay methods for estimating GH (2, 3) which are the most sensitive and accurate now available, depend on the fact that radio-iodinated GH of high specific activity (4) competes with standard or test GH in plasma for binding sites on a 8-globulin in antiserum prepared in rabbits. The competition results in 'bound' and 'free' ^{131}I-GH which are separable electrophoretically and counted for radio-activity. Inhibition curves relating bound : free ratios to standards are drawn and test samples assayed against them. There is good evidence that the assay is specific (5). Reactive material is elevated in acromegaly and is absent after hypophysectomy : jugular vein plasma contains more than inferior vena cava plasma : cross-reaction occurs between plasma samples only from species whose pituitaries contain cross-reactive material : acromegalic plasma acts just as a plasma dilution of pituitary extract.

The survival of GH in plasma has been investigated. Intra-venous injections of GH showed a half life of about 30 minutes (6, 7). Endogenous GH stimulated by hypoglycemia and 'switched off' by glucose and glucagon infusion (8) decreased at a simple exponential rate with a half time of 20-40 minutes.

Plasma GH levels show marked fluctuations. 'Spikes' occur in healthy adults fasting in bed (5). Variations influenced by exercise, nutritional state and sleep are such that only serial estimations on individual subjects give meaningful results about GH secretion (9).

A 70 kg. man may contain 350 g. of glucose and 10,000 g. of fat, yet the importance of FFA as a metabolic substrate has been recognised only recently (10, 11). Triglycerides in fat cells are hydrolysed to glycerol and FA by hormone sensitive lipases (12), glycerol being liberated to plasma and FA being bound to albumin for transport. Plasma glycerol (13) and FFA levels have both been used as an index of lipolysis. Many hormones initiate or contribute to lipolysis : adrenaline, noradrenaline, corticotropin, thyrotropin, thyroxin, corticosteroids, intermedin (α and β forms), glucagon, vasopressin and GH.

In vitro methods have been widely used in the investigation of lipolysis : results must be evaluated with suspicion as awkward but

physiological complexities may be eliminated. However, isolated rat adipose tissue cells, subject to the combined actions of GH and a synthetic glucocorticoid showed a lipolysis that was slow in onset and secondary to RNA synthesis (14). The addition of Actinomycin D, which blocks protein synthesis, prevented the lipolysis. The inclusion of a protein-synthesis delay in the timing of the GH mediated lipolysis of exercise would prohibit any close short-term correlation to energy demands. Human subjects injected with exogenous GH show an initial fall then a delayed rise in plasma FA levels, the rise being maximal at about 4 hours (15, 16, 17).

When subjects perform moderate exercise their plasma FFA levels rise from the basal post-absorptive levels (18). In these experiments mean levels rose from 0.76 to 1.44 m. moles/litre. Turnover of FFA as measured by continuous infusion of palmitate-1-C^{11} with measurement of specific activity of FFA and expired CO_2, is also increased in exercise (10). This increase is gradual and spread over the first hour of exercise, but uptake from the blood doubled almost immediately.

GH levels, too, rise in exercise. The very low basal levels in the resting postabsorptive state rise within an hour of the onset of exercise to a peak of total duration 1-2 hours. Prolonged exercise elicits more peaks. In these experiments (19) the FFA levels rose throughout exercise, but the times of onset of FFA and GH rises could not be compared on account of long sample intervals. Hartog *et al.* (20) using shorter intervals showed small transient depression of both GH and FFA in the first 10 minutes of exercise. Mobilisation of fat revealed by increased plasma glycerol, occurred within 5-10 minutes, whereas GH did not rise until after 20 minutes. This discrepancy in the timing of the two events would seem to eliminate GH at least from the initiation of the lipolysis of exercise.

The elegant human forearm preparations used by Rabinowitz *et al.* (21, 22) to study FA arterio-venous differences over subcutaneous and deep muscular vascular beds. Simultaneous R.Q. and glucose arterio-venous difference determination confirmed the importance of FA as a fuel for muscular exercise. Intra-arterial injection of GH in near-physiological concentrations produced a prompt increase in FA uptake by muscle : subcutaneous tissue released FA after a delay of about 40 minutes. These findings provide a possible basis for the observed fall and rise of plasma FA after GH administration. Once more the considerable latency in GH-induced lipolysis makes it an unlikely contributor to the FA rise of early exercise.

Some of the experiments quoted above arrive at conclusions based on changes in plasma levels, the significance of which should therefore be critically considered. The plasma level of a substance is the net effect of its addition to, and removal from, the blood : a change in plasma level reflects an excess of one over the other. The turnover of a substance may vary independently of its plasma level, e.g. in certain circumstances where lipolysis in adipose tissue and FA uptake by muscle are both raised, turnover will increase while plasma levels may remain constant. Similarly high plasma levels may conceal a low turnover. Hence future attention should be directed towards turnover studies with labelled FA combined with short interval GH estimation.

Plasma FA has a high turnover (10). The human forearm (21) and whole rat experiments (16) indicate that GH can cause an immediate fall in FFA, suggesting an increase in uptake. It is also established that GH causes a later rise in plasma FA attributed to lipolysis in adipose tissue. These two sets of observations make it exceedingly difficult to interpret changes in the plasma FA levels following GH administration or endogenous secretion. Since the hormone is associated with two antagonistic effects on plasma FA due to stimulation of uptake and release it is likely that the lipolytic action of GH might commence much earlier than the FFA rises observed by many workers (15, 23), and that an unchanged plasma FA level might conceal an increase in turnover. Such theoretical considerations provide a basis for the variety of latencies suggested for the lipolytic action of GH. The human forearm experiments eliminate the crude plasma levels and take separate account of uptake and release by measuring A-V differences across subcutaneous tissue, presumed adipose, and deep, muscular, vascular beds. The brief latency observed (40 minutes) is probably reliable.

Growth hormone is released by the anterior pituitary and is distributed to the systemic blood by the venous drainage of the gland and the jugular vein. Once more the instantaneous plasma levels tell nothing of its release and uptake. We do not know the duration of the burst of secretion which gives rise to the GH

peaks found in exercise or basal, fasting subjects. These last 1-2 hours (19, 20) and figures obtained from sampling at intervals of 10 minutes suggest that the rise is steep (20). Most of the rise may occur between two samples, perhaps reflecting pituitary activity lasting seconds, or, at most, minutes. Little significance can be attached to the height of these peaks. Mixing in the peripheral blood followed by distribution to the extracellular fluid and uptake by the tissues will determine the decline of the peak: these factors contribute to the observed half life in plasma, which is 20-30 minutes. This is fairly constant regardless of the physiological circumstances in which GH is administered, suggesting that uptake is not a variable (24). There is no information about its duration of action.

In general, hypothalamic-pituitary neuroendocrine systems mediate control between the CNS, where units of neural activity occupy only milliseconds, and the periphery, where metabolism and structure alter over minutes and years. When exercise commences, GH is liberated and lipolysis occurs. The events may be causally related. In any case, two latencies have to be considered: the first, before plasma GH levels rise, could conceivably be a case of simultaneous release and uptake as discussed above; or it could simply be a delayed GH response. If the former, turnover could be detected with labelled GH though difficult technical problems of estimation and short interval sampling would arise. The second delay, prior to the lipolysis which follows a close intra-arterial injection of GH (21), is well established. Together these latencies appear to disqualify GH from an adipokinetic role linked at all closely to the varying demands of exercise. However, *in vitro* evidence that GH facilitates lipolysis by other hormones (14, 25) suggests a synergistic role: in which case the time relations might be less important.

To summarise briefly: transient peaks in plasma GH levels are regularly seen in exercising adults. *In vitro* evidence suggests an association, involving other hormones, between GH and lipolysis. The maintenance of lipolysis in continuing exercise may depend in part on this effect. However, from the evidence concerning the onset of lipolysis and GH secretion on the commencement of exercise, it is not possible to conclude that GH secretion initiates lipolysis in exercise.

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The Itch

Authors, and those too, of no small note contend for animalcules being the cause of this distemper; and indeed it is hard to call in question the veracity of such Gentlemen, who have given us not only the figure of these little creatures, but also assure us that, upon further search they discovered the Eggs from which they are produced by generation, as fast as Lice. Be this however as it will, I should give it as my opinion that still these animals are not to be looked upon as the cause, but rather the effect of this disease.

—*from the Society's collection of Dissertations, 1772.*

THE DEFENCE MECHANISM IN MALIGNANT DISEASE

R. D. Hunter, B.Sc.

From a dissertation read before the Society on November 6th, 1968

The original suggestion implicating immunological factors in the natural history of malignant disease has been ascribed to Paul Ehrlich(1). Confirmation of this concept has waited fifty years for developments in knowledge and technique but its application allows not only some understanding of observed phenomena, but speculation on a rational approach to treatment and on a scientific establishment of the aetiological factors involved.

Traditional teaching defines this group of conditions by the type of tissue change involved, the degree of differentiation and extent of spread. From these a prognosis is assessed and the clinical picture tends to be one of steady progression, interrupted by therapeutic endeavour, but culminating in the death of the patient. Variations on this picture are seen in clinical practice.

CLINICAL PHENOMENA

Everson(2) has collected a series of 130 fully documented cases in which unequivocal regression of the neoplasm was observed in spite of no effective treatment. Histologically proved metastases have been seen to regress after treatment of the primary lesion (3), and metastatic deposits from breast neoplasms often recur many years after treatment of the primary lesion (4).

Considering the opposite end of the spectrum, transplantation of malignant neoplastic tissue from one human host to another has been a notoriously unsuccessful procedure(5) but transplantation of tissue containing neoplastic cells in the face of immunological suppression has resulted in the rapid proliferation of the neoplasm within the new host (6, 7) and apparent reversal of this phenomenon has been seen when the suppression was discontinued(8).

These examples, implicating immunological reactions between the host mechanism and the neoplastic cell, imply some alteration in the antigenicity of the neoplastic cells. Specific tolerance, by the host, of its own tissue antigens is a very well substantiated thesis(9) and the absence of them has been demonstrated for a variety of neoplastic tissues(1). Evidence for the development of new antigens has been sought for in investigations examining both specific effector mechanisms of the immunological system; humoral antibody and the immunologically competent cells(11).

In human disease there are examples of the detection of specific antibody to neoplastic cells(10) and of the qualitative relationship between them and the extent of the disease process(11). A strong case has been made on the basis of animal experiments, implicating humoral antibody in the natural history of neoplasia(12) but the cellular nature of the infiltration, when viewed in the light of the lack of role for antibody in the homograft reaction(13), and recent concepts of the possible role for humoral antibody in the consequences of cell death(14) makes any interpretation of the results impossible at present.

ANIMAL EXPERIMENTS

Unfortunately the function of the immunologically competent cells has proved more difficult to study and no reliable direct test of this mechanism has become available. The method which has given rise to the breakthrough in this field has been the transplantation of neoplasms between members of allogeneic strains of animals. Their genetic similarity allows tissue to be transplanted from one to another within the strain with impunity, but Foley(15) demonstrated that a carcinogen induced neoplasm would be rejected if the animal had previously been exposed to the same neoplasm. This rejection was shown to be a function of sensitized lymphocytes(16), thus conforming to the criteria for a homograft reaction, i.e. different antigens must have been present. The work has been confirmed with different animals and different carcinogens (17, 18) with the additional demonstration of the antigenic independence of each individual neoplasm.

Repetition of this work with viral induced neoplasms in animals has allowed the demonstration of tumour specific antigens(19) as before but a very significant difference became apparent when the new antigenicity was shown to be identical in all the neoplasms induced by the same group of viruses(20) and different when various groups were contrasted (21).

In view of the artificial method of neoplasm induction used in these experiments the results might be viewed with some suspicion but the demonstration of this rejection phenomenon in a spontaneous tumour arising in an allogeneic strain of animals(21) and in recent sophisticated experiments involving human neoplasms(23) makes the acceptance of the general concept much easier.

IMPLICATIONS ON EARLY NEOPLASM GROWTH

While the reality of neoplasm specific antigens accords with experimental results and explains clinical phenomena, the presence within an immunologically mature individual of a viable antigenically distinct clone of cells demands some explanation.

The dose of antigenic neoplastic cells necessary to stimulate graft rejection is critical and overwhelming by large implants(24) has its corollary in infectious disease. However the viability of a minute implant of antigenic neoplastic cells(25) and the possibility that neoplasms are the descendants of a single mutant cell (26, 27) complicates the picture.

The lack of association between antigenic change and malignant change, as evidenced by the carcinogen experiments(17), suggests that loss of cell specific antigenicity may not be a universal concomitant of malignant transformation. The antigenic change may be small and not provide the necessary stimulus to summate in a homograft reaction(13) or produce physiologically poor antigenic groupings(1).

It has also been pointed out that serum infusions may stimulate neoplasm growth and the possibility that antigen expression may be prevented by blockage of the sites must be entertained(28).

Looking to the defence side, the possibility of poor immunological competence in patients with neoplastic disease has been considered but, using the present rather crude methods, no defect has been found in patients with early neoplastic disease(5) defects only appearing as the disease progresses(29).

The growth of antigenically distinct cells in the face of apparently good immunological function remains, at present, unexplained but it seems probable that it is a manifestation of a multifactorial system invoking many of the above factors, and others as yet undiscovered, in different proportions under different circumstances.

CINICAL CONSEQUENCES

1. Theoretical

One consequence of these findings has been the concept of Immunological Surveilance (26) in which the antigenically distinct mutant cell is picked out and destroyed by the immunological mechanisms. Indirect evidence suggesting that this should be seriously considered comes from the recent reports of the appearance of reticuloses quite out of proportion to the expected incidence, in patients on continuous immunological suppression (30, 31). It has also been pointed out that the incidence of neoplastic disease rises as immunological function falls in old age(26).

This exciting concept may not stand the test of time but it seems likely that with the realisation of the ability of one challenge to

influence general immunological responses for some time(32) and a better understanding of the phenomenon of specific tolerance(3) host factors may find some place in the explanation of the successful growth of the early neoplasm.

2. Treatment

A logical consequence of these results has been the suggestion that immunological methods might be used in the treatment of malignant disease. Infusions of splenic tissue (33) and sensitized lymphocytes(34) have been tried in terminal patients with some apparent success. This is an interesting phenomenon but the lack of overt impairment of the immunological response in patients with early neoplasia(5) militates against such an approach being of any help when curative procedures are being considered. There are also dangers of the selection of non-antigenic mutants, antibody blockage of antigen sites, and the induction of tolerance, all of which have been seen in the experimental model(28), and which call for a better understanding before methods of specific response stimulation can be used in man. Further developments are to be expected as the specific nature of the response of the immunological system when contrasted with the systemic administration of a drug makes this the theoretical method of choice.

Preventive procedures also call for some attention. Immunosuppression is the accepted treatment of the rejection of human homografts but the recent appearance of neoplasia (30, 31) soon after the onset of treatment, in what is a young population, must give rise to concern. Advances in tissue typing should soon eliminate the necessity for this approach but it must be remembered that the therapeutic arsenal of malignant disease contains many immunosuppressive agents(35). One of these, 6-mercapto-purine has been shown to cause tolerance induction to neoplastic antigens(36) and, in therapeutic doses, to convert a tumour rejection reaction into acceptance with consequent death of the animal(37). The relative importance of the immunosuppressive effect and the therapeutic effect is probably weighted heavily in favour of the latter but this should not allow the former effect to be ignored.

3. Aetiology

One final aspect of neoplasia which has been influenced by the study of antigens on neoplastic cells has been the consideration of the aetiological factors in human disease. With the difference between the neoplasm specific antigens following carcinogen induction and the group specific antigens seen after viral induction in mind one group of workers, led by Kleine(12), have studied the human disease process in which the possibility of a viral aetiology has been most entertained — Burkitt's Lymphoma. Their results showed cross reactivity between the cellular antigens of different patients. Interpretation has been complicated by the demonstration of the presence of three different viruses in lymphoma tissue(38), the recognition of the parasitism of neoplastic tissue by viruses, and the implication of one of the viruses in a common benign lymphoreticular disease(39) but the methods involved may lead to a breakthrough in knowledge when these phenomena are better understood.

CONCLUSION

It would be foolish to claim that the demonstration of neoplastic cell antigenicity has contributed significantly to the treatment of human disease to date but, apart from offering tremendous hope of advance in the near future, it allows consideration of the problem, not as a one-sided invasion, but as a dynamic situation in which host mechanisms may be playing a significant part.

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Rondomycin?

What are the medical virtues of Musick and in what diseases is it to be recommended?

—*title of Dissertation to the Society, 1752.*

OPINION

Professor Christian Barnard

Organ transplantation has evoked such mixed and even violent reaction that it would seem worthwhile to explore the ethics governing it — and to do this by examining the three major areas of contention : the act itself, the recipient and the donor.

IS TRANSPLANTATION ETHICAL?

News coverage of transplantation in the popular mass media has been widespread, enthusiastic and, unfortunately, too often sensational and misleading. It has been misconceived in certain sections of the public both as a panacea and as an unethical and unjustified form of treatment. Neither assertion is accurate.

Within our currently limited understanding of immunological attack on an allograft and our inability to prevent such an onslaught, the transplantation of any organ must be accepted as palliative therapy — not a final cure. It achieves palliation which equals, if it does not surpass, some forms of palliation which have been accepted for many years as the only way to deal with malignant diseases. This being established, one cannot accept as unjustifiable or unethical the palliation of symptoms and extension of life itself.

A frequent criticism is that the manpower and the financial expenditure involved in transplant programmes far outweigh the results obtained, and that other medical services have a more urgent and real claim to the financial and intellectual effort needed for transplants. This sort of criticism is extremely conservative and dangerously short-sighted. Similar attacks were once levelled by similar critics at open-heart surgery using cardiopulmonary bypass. This happened in the early days of this new technique, but as the surgeons and scientists learned more about heart-lung machines and the management of patients seriously ill from heart disease, methods and apparatuses were simplified and the techniques became more widely applicable.

To curb transplantation at this stage would be to strangle one of the most promising and exciting fronts of medical endeavour of this century. From the experience gained in the problems of rejection, methods of immunological control will be improved and vital organ replacements will become a routine and life-saving procedure. To deny medicine its full thrust in this direction would be irresponsibly short-sighted. Indeed, it is difficult not to conclude that any withdrawal from this new frontier would be professionally unethical. We have only to continue transplantation on a most active scale.

DOES THE RECIPIENT RECEIVE AN ETHICAL TREATMENT?

It is currently accepted that a patient should not be submitted for organ transplantation

unless he suffers from an irreversible disease of the organ to be transplanted; that conventional therapy is of no further avail; and that the patient has progressed to the terminal stages of the disease — in blunter terms, he should be dying. Allograft replacement of such an affected organ may offer the patient a significant extension of life. Renal recipients may look forward to several years of extended life.

It is still premature to evaluate heart and liver transplants, but we should note that there are recipients of heart and liver grafts who are in their second post-transplant year — and not without dramatic relief. Not only is there extension of life, but also a significant palliation of life-crippling symptoms. The cardiac recipient exchanges the horror of terminal cardiac failure for a life similar to that of a vigilantly controlled diabetic; the distress of uraemia and frequent haemodialysis is exchanged for daily drug control and a full life.

IS OUR ACQUISITION OF DONOR ORGANS ETHICALLY ACCEPTABLE?

For many years both medical and lay public have accepted that after the certification of death by three well-known criteria — brain death, no sponanteous respiration, and absence of cardiac activity — a post mortem is performed and the heart, instead of being placed in a bottle, is transplanted in another body in an attempt to save a life or alleviate suffering. There is no ethical principle which establishes this act as unacceptable, or immoral. Inevitably, one can only conclude that it is unethical to allow such organs to putrefy with the cadaver, thus denying a potential recipient an extension of life.

There are people who accept this argument and yet voice real mistrust of the management of the donor before the certification of death. These misgivings are entirely unfounded. Years before surgeons embarked upon the transplantation of cadaver organs, neurologists and neurosurgeons concluded it was futile to keep patients alive — once there is undeniable and irreversible brain death. In short, it has been universally acceptable that at this stage artificial maintenance of life may be terminated. Moreover, throughout the world responsible medical and legislative groups have defined the moment of death and the handling of a potential donor. Further, with heart transplants even greater care is taken to handle this problem most ethically.

Certain fundamental principles of donor organ acquisition should be emphasised. All patients in need of resuscitation and special care must receive this with the utmost skill and efficiency available today, and potential donors should be admitted under the care of doctors who are not involved in transplantation.

This separate group of doctors must decide when treatment is of no further use or avail, and should therefore be discontinued or not instituted. They may then discontinue or withold treatment when they decide that gross loss of cerebral function has occurred and is permanently irrecoverable. Before coming to this decision there must be a positive clinical diagnosis which will permit prognosis. Also, there should be instituted all appropriate clinical investigations which might indicate a remediable or reversible condition.

Cerebral death should be diagnosed on neurological, electroencephalographic, circulatory and respiratory criteria, using the best available apparatus and skill. If these criteria are fulfilled, the patient is declared dead and only then is it possible to take measures to obtain viability of desired organs. At that stage, a donor may be transferred to the transplant intermediary or referee. There seems little doubt that this is the morally and ethically acceptable sequence of events for this crucial point in the transplantation of an organ.

Because it is desirable that the results of animal and laboratory experiments be applied to human beings to further scientific knowledge and to help the suffering of humanity, the World Medical Association has prepared recommendations as a guide to each doctor engaged in clinical research. One of these recommendations is that in the treatment of the sick person, the doctor must be free to use a new therapeutic measure if, in his judgement, it offers hope of saving life, re-establishing health or alleviating suffering. There is no doubt in my mind that we had reached this point in organ transplantation.

REVIEW

● It was with mixed feelings that we came to the first part of our sale at Sotheby's. We could not be but pleased that four years of careful thought and debate, then of negotiation, had come to an end: but the pleasure was mixed with sadness that the library was being split up irrevocably under the auctioneer's hammer. Economic logic was not enough to fully cover the feeling that had bound the books to the Society's history.

The sale began at 11am precisely, on Monday, 10th February. By 1.30pm the same day the books had realised £21,000: and on the following day a further £18,000 had accrued in less than two hours. The total sum from the first sale therefore does much to justify the decision to sell by auction, and justifies completely our hopes that the total sale should reach something more than £100,000, if not equalling the £120,000 that was turned down early last year when an American institution had offered to buy the whole collection.

The principle that the books should be available to all, and particularly British collectors has been justified too. Although the biggest buyers were naturally the dealers Dawson and Rota, a number of the more important works were in fact acquired by private collectors. Most notable was the successful bidding by a London professor of Chemistry for nearly all our collection of the works of Boyle as well as for other works on chemistry such as Davy's "Researches Chemical and Philosophical" and Clarke's "The Gas Blowpipe or Art of Fusion".

There were a number of surprises which made the sale exciting as well as successful. Ampère's "Theory of Electrodynamic Phenomena" went for three times its valuation price, at £450, Baer's "De Ovi Humani" reached a staggering £1600 having been valued at £300, and a dedicated copy of Claude Bernard's "De L'Origine du Sucre" brought £1200.

As expected, Bright's "Reports" reached four figures, but better still brought its highest recorded price at £1600 for Messrs Dawson.

All this on the first morning. And the second morning was just as lively; Carpue's "Restoration of the Nose" climbed to £1200 as had Caesalpinnus' "De Plantis" five minutes earlier. Dawsons were successful in their bid for Floyer's "Pulse Watch" at £450, three times valuation.

Lot 438, a very extensive collection of about 3000 Edinburgh Dissertations (not the Society's Dissertations) was withdrawn at the last moment when Sotheby's discovered two more cases of books in their store, including a number of further dissertations, and these will be re-catalogued for a later sale. Lot 468 was withdrawn completely, to be returned to the Society; this was a 1790 narrative "of some late injurious proceedings of the managers of the Royal Infirmary against the students of medicine" which included a manuscript minute of a meeting of the students concerned in the Society's Library.

The auctioneer was Lord John Kerr. While his manner was cool and deliberate on his rostrum he later confessed that this had been for him a most exciting auction: he himself had received bids for every lot and from all over the world, and many it seems from Life Members of the Society; Dawsons too had an unusual number of commissions, which all went to make the sale the more exciting and successful.

The next sale will be in July, when we will once more put into effect our massive mailing machinery to ensure that each Life Member

receives both notice of sale and his souvenir catalogue. A third sale should take place in the autumn. Sotheby's have described the first sale as "fantastic" both in the pattern of bidding and in the prices realised, and are optimistic for the final sale figures; we in turn are satisfied that ours was a correct decision.

● Everyone who has ever been to a President's Dinner knows that it isn't really the President's at all. The dinner is ours, the guests, whilst the Presidents, rigid with apprehension, which the wine does nothing to allay, come along merely to entertain and amuse us with their witty speeches. This is part of the tradition of the occasion; an integral feature of the cosy atmosphere, of the whole déjà-vu experience.

The atmosphere and the essential characteristics were the same this year as always: one was sitting by the same nice people, the food was the same, and the conversation hadn't changed much either. It didn't really matter. As one slipped into the depths of physical contentment, so old faces became younger and young faces achieved a surprising maturity; the talk seemed to sparkle more and even the portraits on the walls looked fractionally less ugly.

Sir John made a serious speech which was rather moving; Professor Perry didn't, but he was about to leave Edinburgh, so his made us sad too. We all applauded furiously, and thought what splendid men they were (which, of course, they are). Dr. Simpson's speech was a funny one, and we all laughed immoderately. However the greatest success of the evening was Miss Duncan, whose charm enveloped us all like a tangible cloud.

Rapport, en masse, is a rare phenomenon, but we achieve it at our dinner. We will next year too; it's one of the pleasanter inevitabilities of life.

● Once more we thank our honorary editorial board. Also Miss Joan Ross and all the typists in Clinical Surgery and Miss Harkins for so cheerfully doing all the extra work that we have burdened them with over the past year.

THE CONTRIBUTORS

DR. HENRY WALTON *is the consultant in administrative charge and director of the University Department of Psychiatry at the Western General Hospital. The second part of his article, written specially for* RES MEDICA, *gives us a great deal of insight into the way in which the Psychiatrist obtains his information from the patient.*

MR. TOM HAMILTON *is Senior Research Fellow in the Department of Clinical Surgery. In 1964 he was in the Ben May Laboratory for Cancer Research under the direction of Dr. Charles Huggins, Nobel Prizewinner 1966 for the demonstration of hormone dependence in cancer. Tom Hamilton's major interest is the endocrine and environmental influences upon human cancer — particularly of the breast.*

PROFESSOR CHARLOTTE AUERBACH *was elected F.R.S. in 1957 and was appointed to the chair of Animal Genetics in Edinburgh in 1967. She is well known for her pioneering work on the Chemical Induction of Mutations and her article is based on a very well received address, which she gave to the Society in November last year.*

DR. H. W. C. GRIFFITHS *is Consultant Anaesthetist in the Royal Infirmary, Edinburgh. He carries on the Edinburgh tradition of the use of chloroform in anaesthetics. His article lucidly sets out the case for chloroform with masterly handling of the historical controversies surrounding this subject.*

COLIN CURRIE *is now in Final Phase having spent a year doing an Honours Physiology degree. His writing outside the scientific field is notable for its incisive aptness. His interest in Growth Hormone is said to have begun with a 28 mile run, complete with respirator, during his Physiology days.*

ROBIN HUNTER *is the 1968-69 Senior President of the R.M.S. and also took his Honours Degree in Physiology. He has been a very popular and efficient President and his article on the immunological aspects of cancer originates from a dissertation given before the Society on that subject.*

PROFESSOR CHRISTIAN BARNARD, *who is Professor of Surgical Science at Cape Town University Medical School, needs no introduction to our readers. Many will have heard him speak in Edinburgh when he was here as a guest of the Royal Medical Society and we welcome his views on the ethical problems of transplantation.*

Fire, Earth and Water

Fire, Earth and Water are the first Materials of which all Sensible Bodies are composed. To these three classes by properly conducted Processes the most Compounded Body can be reduced, and upon the various combination of these three arises all the surprising Variety to be found in the Subjects of Natural History, therefore the different Virtues depend not so much on the Bodies themselves as on their different Union one with another.

Chemistry either unites Bodys that were before separate or separates those that were before united therefore every Process makes a new Medicine as it causes a new Change or to speak as above a new Virtue.

—from the Society's collection of Dissertations, 1751.

BOOKS

New Aspects of Human Genetics. British Medical Bulletin, January 1969.

The B.M.B. is published tri-annually by the Medical Department of the British Council; each volume consists of a series of articles by acknowledged experts on growing points in selected fields and this volume is no exception. It would seem presumptions to criticise such a journal and one can simply give an indication of the range of material covered.

The articles in this issue consider many aspects of human genetics, from 'Enzyme and Protein Polymorphism in Human Populations' by Professor R. H. Harris, to 'Genetics of Common Disorders' by Dr. C. O. Carter. Inborn Errors of Metabolism are well covered from a number of aspects, as are chromosome abnormalities. Two of the articles on cytogenetics are written by experts from the Edinburgh M.R.C. Unit on clinical and population cytogenetics: 'Human Population Cytogenetics' by the late Professor W. M. Court-Brown and Mr. P. G. Smith, and 'Structural Abnormalities of the Sex Chromosomes' by Dr. Patricia Jacobs. The Bulletin also includes discourses on the genetic aspects of haemoglobinopathies, the porphyrias, blood-groups, autosomal imbalance, mosaics and chimeras, and reciprocal translocations.

All of these articles contain very concise, highly concentrated information, couched in the jargon of each speciality. This is definitely not bed-time reading, but more reference material for those with a specialised knowledge of, or keen interest in, human genetics. Not a volume for the average medical student unless he has a great enthusiasm for the subject.

S.J.U.

The Eye in General Practice (5th. Edition) by C. R. S. Jackson. E. & S. Livingstone Ltd. 30/-.

Without doubt, this book fulfils very adequately the need for a concise textbook of ophthalmology for the general practitioner. In particular it emphasises the need for urgent attention to certain disorders and stresses the dangers of indiscriminate use of local steroids.

Dr. Jackson's book is also most suitable for the undergraduate's first steps in ophthalmology, being sufficiently short and readable to satiate the student's interest without overtaxing an appetite already curbed by pressure of other specialities. However, the student will have to supplement his reading by attention to colour slides of ocular conditions and by examining as many patients as possible, for there are only 44 figures (including but 6 fundal photographs). It is appreciated that a book costing only thirty shillings cannot possibly contain large numbers of photographs, but the priorities for inclusion are somewhat incongruous. The presence, for example, of a photograph of a conjunctival mole and two essentially similar pictures of both synechiae and acne rosacea, at the expense of any diagram of the mechanism of glaucoma or naso-lacrimal obstructions.

This latest edition contains one less figure and about ten changes in the text. The most significant of these are a section on welder's flash, an extra paragraph on the implications of aphakia, some aspects of modern treatment of detachment and emphasis on the urgency of treatment of temporal arteritis by systemic steroids in order to prevent loss of sight.

Despite minor criticisms, this book is to be highly recommended.

D.McL.

Recent Advances in Pharmacology (4th. Edition). Edited by Robson & Stacey. J. & A. Churchill, London.

Since the production of the third edition of this review, in 1962, pharmacological research has accelerated explosively, both within the narrow discipline, and, divergently, towards other scientific fields. It is therefore a particularly pleasant surprise to find that the 4th. edition retains the essential quality of its predecessor — the concise, yet comprehensive and vital, presentation of relevant material. This has been achieved by inviting experts to contribute articles on current work in their particular fields. As a result the chapters are of a uniformly high standard, and yet presented with individual emphasis.

The most casual glance — and the material deserves much more — indicates at once the potentially wide appeal of the book. Aspiring toxicologists will appreciate the many illustrations of the metabolic pathways of drugs. The relationship of the clinical significance of calcitonin and gastrin to the study of their basic physiological rôles is clearly shown. Professor Horton accounts enthusiastically the rapid development of prostaglandin biochemistry (honours pharmacology students please note!). Although the biomathematics of drug-receptor interaction is patently for the expert only, the pharmacology of the central nervous system, the subject of so much study, is abbreviated to 80 pages of introductory reading for the senior student of physiology or pharmacology.

The section on immuno-suppressive drugs seems too brief, and there is nothing of oral contraceptives or drugs of dependence. However this is small criticism of a textbook which admirably succeeds in lucidly dovetailing basic knowledge with future possibilities. The popularity of this book can only increase.

J.P.

Body Fluids in Surgery (3rd. Edition) by J. Wilkinson. E. & S. Livingstone Ltd.

This invaluable book which is recommended to students at Dundee Medical School, is a clear concise account of the normal and abnormal in clinical chemistry. The first half of the book contains the physiological mechanisms used by the body in control of a dynamic milieu interieur. Ionic equilibrium and buffer systems are illustrated by simple explanatory diagrams.

The remainder builds on the first few chapters and discusses the effects of stress due to loss of fluid, injury and disease in the adult and child. The final chapters give a brief summary of the diagnostic criteria in fluid and electrolyte imbalance including the drugs and fluids available for their correction.

Dr. Wilkinson's lucid and understandable account of this complicated subject results in a book that should appeal to a very wide readership.

C.M.L.

The Logic of Medicine by D. A. K. Black. Oliver & Boyd Ltd. 7/6d.

Employing a semi-scientific format, as with fertilizing scientific writing with choice references, serves a genuinely useful purpose of reference or merely adds authority to platitude. As one reads further into this book several questions come to mind. Who was it written

for? Why was it written? Returning to the preface we find Professor Black stating "In talking to scientists and educationalists, I became conscious that they are unaware of the exacting challenge which medicine offers to the intellect".

Is this the reason? To convince the rest of the intelligentsia that doctors think and that science has finally permeated through to them. Certainly, even for the first year student, this paperback has little medical appeal. For the layman? The intelligent layman? Perhaps enjoyment of the quasi-medical. Perhaps a little insight — but not much.

A.I.D.

A Manual of English for Overseas Doctors by Joy E. Parkinson. E. & S. Livingstone Ltd.

The Royal Commission on Medical Education said of overseas medical students in its report that 'many lack a quick understanding of the idioms, allusions and variations of intonation used by patients, or in lectures, demonstrations and seminars, although they can cope quite well with social conversation or a medical text'.

Miss Parkinson therefore wrote this book — a very small paperback one — to provide aid for such people. On first opening it the English student might be rather amused — but let him not be so proud — he should read it carefully. There are words and expressions in the colloquial English section which I have never heard before and some which I have heard for years and of which I have never known the significance until now. It is such a good idea to include the sort of phrases which some of one's patients are likely to use, which are not always strictly polite and, at times, incredibly vulgar.

There are sections on letter writing, Medical abbreviations and several examples of patient-doctor dialogues. All very useful for the foreign student, who will also find the chapter on the language of drug addiction of great interest. This discussion makes fascinating reading for many of us, foreign or not, who are not already drug addicts.

This is an excellent book, thoroughly recommended for overseas students, and for the indigenous medical population.

W.D.L.M.

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