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ASPECTS OF OBESITY

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The topic of obesity could provide material for a series of symposia. Personal prejudice has largely determined the aspects chosen for discussion here, and these are intended to demonstrate features bearing on our understanding of the nature of this disorder, which, as is generally recognised, has such profound medical and social implications. Adiposity itself is less of a problem than the sequelae and complications which so commonly occur. The epidemiology of obesity will not be dealt with now, but a moment's reflection on the morbidity and mortality associated with being overweight will suffice to emphasise the importance of even a single example such as diabetes mellitus.

In the studies to be discussed the necessity for a definition of obesity naturally arises, but this need not be laboured. Tables relating height and weight, sex and age, are readily available. These tables usually provide average weights based on height. It might be argued that an average body weight is less suitable than an ideal weight as a basis for investigation and for planning treatment. Tables of average weights are based on actuarial analysis of

previous experience, and these show a tendency for most people to put on weight with advancing years. Such a concept appears to condone an increase in weight that may indeed be harmful. At present it is impossible to assess the contribution made by coincident factors such as diminishing physical activity to the disabilities often attributed directly to obesity.

Other standards have been proposed from time to time to distinguish the normal from the obese, and these are usually based on measurements or estimates of the amount of obese tissue in the individual. Some of these techniques are as simple as measuring the thickness of skin folds with a calliper in standard areas, while others are based on the volume of distribution of deuterium oxide or tritiated water which will equilibrate with the total body water and from this the lean cell mass and thus by difference the amount of adipose tissue can be determined. Weighing under water will also provide an estimate of body fat. The choice between these and other methods is not critical, however, for the purpose of this paper. In studying obesity it is more profitable to select groups of individuals who clearly transgress the bounds of any normal range, so that by any standard they are clearly abnormal.

When confronted by an obese patient, and faced with the necessity of advising treatment, two immediate problems present themselves. Firstly, and as a matter of expediency, what advice should be offered? Secondly, why has the patient become obese? In seeking to rationalise the second question we may answer the first more effectively.

Fundamentally, it may be claimed, the fat are overweight because control of the balance between energy intake and output is defective, and the balance remains positive too often for too long. From this premise it may be argued reasonably that the loss of metabolic equilibrium could occur because the intake of energy was in excess of needs, or alternatively, and even in addition, that the output of energy was insufficient to deal with the load imposed on the intake side of the equation. These are really about the only assumptions that can safely be made at present.

The contribution of energy output as a mechanism for maintaining a steady weight is difficult to study because of the technical problems involved, and particularly because the investigation must be extended as far as possible in time in order to take account of fluctuations that are constantly occurring. Variations in the amount of energy lost in the urine and stools can be discarded as factors of importance in most cases. Variations in the physical activity of the patient however certainly cannot be ignored. Even when it has been shown that the obese exert themselves less than those who remain thin, the problem remains whether this economy of effort is cause or effect. Only prospective studies would provide an adequate answer to this question and such an undertaking may be well nigh impossible. Several workers, notably Stunkard, a psychiatrist in Philadelphia (Chirico and Stunkard, 1960) and Mayer (Johnson, Burke and Mayer, 1956) in the Department of Public Health in Boston, have shown that on average the obese exert themselves less than do their more slender controls. This applies in children as well as in adults, and appears to affect girls more than boys. It may be noted however that the fat patient does more work than the lean in moving the same distance, for the most obvious of reasons, namely that the bulk to be moved is greater.

Thus the conclusion stands that many fat people spend less energy on kinetics than those who are thin, and they apparently fail to restrict their energy intake appropriately, and therefore become or remain obese.

For 50 years or more, suggestions have been made that the normal individual has a metabolic "bypass" denied to the obese, for burning off surplus energy, and that for this reason the fat man who eats more than his energy output would require will accumulate adipose tissue, while the thin man with his "bypass" remains thin in spite of eating more than is necessary to meet his strict requirements. This postulated mechanism was described as "luxus konsumption" by Grafe (1933) but it has never really been demonstrated with conviction. Indeed more evidence has been adduced against it than in its favour.

Two further aspects of the output side of the energy equation should be mentioned here. The first of these is exemplified by a group of seven grossly obese patients who were studied most rigorously under hospital conditions, but in a general ward. Their diets provided between 370 and 550 kcal. daily only and by encouraging them to take exercise until they were walking as much as ten miles daily, these patients were able to dissipate sufficient energy to achieve negative energy balances to the extent of 2500-3000 kcal. daily. As might be predicted they all lost very substantial amounts of weight in periods of six weeks study, the

losses ranging between 13.4 and 17.3 kg. This of course represents rather an unusual state of affairs and would not normally be practicable or perhaps advisable except under strict supervision. Only the obese who remain mechanically intact are capable of this degree of activity, but it serves to show what can be achieved in this way.

The second aspect concerns the effect of exercise on appetite. The amount of exercise one takes will affect the debit side of the energy equation, while the appetite will be all important in determining the energy credit, assuming that free access to food is available. Mayer and his colleagues (1954) carried out experiments using rats in cages equipped with treadmills so that the animals were exercised daily for variable periods. With free access to food, over a wide range of energy expenditure, the animals matched their intake of calories against their energy output in such a way that they neither gained nor lost weight. Only at either extreme of physical activity did this nicely balanced mechanism show signs of breaking down; at one end because of exhaustion from overwork. At the other end, and infinitely more important for our understanding of obesity, when the animals' opportunities for exercise were restricted, their food consumption rose above their requirements, and as might be expected, their weight began to increase.

The implication is clear, namely that energy intake will match the output, provided the amount of physical exercise taken does not fall below a certain minimum.

Some of the other factors bearing on the rate and amount of weight loss occurring on reducing diets are illustrated by the case of Christine E. (Figs. 1 and 2). This patient was weighed daily for a period of some 17 months, while she was on a diet usually providing approximately 400 kcal. daily: occasional changes were made for special purposes. It may be added that in spite of the effort and expense involved in supervising her diet and activities while her weight was reduced to less than half her initial weight, she has since regained almost her original weight and has now become a diabetic. Before the end of the study, because of persistent suppuration, it became necessary to excise her umbilicus, and this was removed along with a layer of fat weighing approximately 12 lbs.

During the time covered by Fig. 1 her weight was reduced from 156 kg. (344 lbs. or 24½ stones) to 76 kg. (168 lbs. or 12 stones). Such a fall is equivalent to an average daily loss of
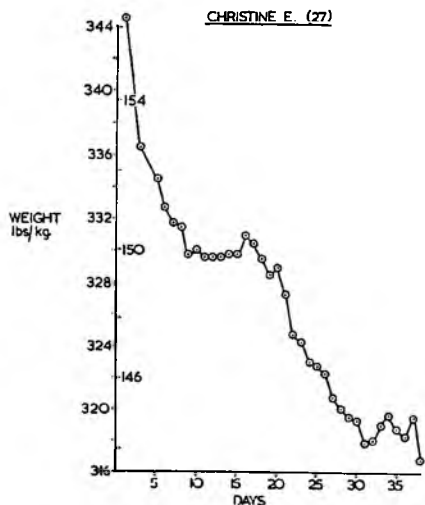
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Fig. I. Loss of weight by an obese patient on a diet providing 400 kcal daily.

Fig. 2 Daily weight changes in an obese patient during the first 5 weeks of a strict reducing regime.

150 g. or 0.33 lb. Most of the points in Fig. 1 represent intervals of one week. It will be noted that the fall in weight tends to be stepwise, and indeed at one stage for a period lasting several weeks she failed to lose any weight at all, although adhering to the usual regimen. In spite of fluctuations of this type however, the overall loss of weight was steady throughout. For a phase of 8 months approximately, records were kept of her menstrual periods, and it will be seen again that about the time of onset of her period, a sharp rise in weight usually occurred, subsiding again thereafter with an appropriate increment in weight loss, to resume the steady decline.

In Fig. 2 the daily weight changes are shown that occurred in the interval following her admission to hospital. The striking alterations in the rate of loss of weight may easily be seen. From the point of view of obese patients taking strict reducing diets, it is most important that they should be told what they may anticipate when dieting conscientiously. Unless this is done they become disillusioned when the rapid initial loss of weight of the type illustrated in Fig. 2 fails to continue, and thereafter abandon the very real effort involved in adhering to a regimen likely to produce consistent results. Even more discouraging are the phases of water retention also illustrated, when not only is loss of weight not continuing but gains in weight are occurring, sometimes for several days in succession. Phases of this type may persist for 10-14 days or more, and unless the patient is constantly reminded that this failure to lose weight is temporary only, that it is relatively common and will be succeeded by a compensating period with an increased rate of weight loss, only the stupid or unnaturally stoical patient is likely to continue with dietary restrictions.

The mechanism responsible for the water retention accounting in turn for these rather anomalous changes in weight has not yet been identified.

Studies by Russell (1962) on sodium and water excretion by obese patients on reducing diets strongly suggest that the surplus water accumulated in the circumstances described is accompanied by sufficient sodium to keep the additional water retained isotonic with extracellular fluid: from time to time the excess of both is released and excreted. There are grounds for suggesting that something similar may happen when more generous diets providing up to 1000 kcal. daily are in use. In these circumstances, feeding a high carbohydrate diet enhances water retention, a high fat intake on the other hand will promote a more rapid rate of loss of weight for a few days, until a new equilibrium has been established, and weight loss will then continue predictably, depending on the energy balance.

Studies undertaken in a number of centres bearing on the weight reducing properties of a variety of diets would indicate that when adhered to strictly, and excluding short term differences due to variations in water balance, the ultimate rate of loss of weight depends upon the caloric content of the diet, and not upon the form in which these calories are taken.

It should be added that while the energy content of food is all important in maintaining weight at a constant level, the relative content of carbohydrate, protein and fat in the food eaten are probably of minor importance except to the extent that they affect the palatability of food and therefore the appetite of the patient. In the longer term, however, the reverse would be true when the patient or subject has freedom of access to food. The satiety value or appetite suppressing properties of food must be of the greatest importance in determining when a person with free access to food will stop eating. Our ignorance in this regard must largely be attributable to the formidable problem of demonstrating in man what it is that stops him eating. We know that in animals hypothalamic centres for eating and for satiety can be demonstrated, and that exercise and temperature, solitary confinement or group feeding, restricted periods of feeding or continuous access to food can all affect the issue quite profoundly.

The heat conserving properties of a layer of subcutaneous fat and the effect on body temperature was studied recently by Quaade (1963) in Copenhagen. He measured the skin temperature on the surface and the temperature deep to the abdominal layer of fat in groups of obese, normal and thin individuals, and showed that although the abdominal temperature in the fat man is slightly higher than in the thin, the skin temperature is lower in the fat. There are several possible explanations for these differences, but one reasonable interpretation would be that a heavier layer of surface fat is a more effective insulation against heat loss than a lighter covering of this type. Such a factor might contribute to the difficulty some patients evidently have in dissipating surplus energy.

There are relatively few studies available of protein metabolism in the obese and such as there are indicate that it may be normal. This conclusion, however, should be accepted with reserve for the present. Our own investigations suggest that obese patients lose little protein when taking severely restricted diets.

The obese also show an unusual resistance to the development of ketosis: unusual in the sense that under dietary conditions and conditions of exercise, where the lean can be expected to excrete relatively large quantities of ketone bodies, the obese fail to do so. This too is characteristic of the maturity onset insulin resistant adult diabetic who is usually obese, but the protective factor possibly common to these two important conditions and responsible for their relative immunity to ketosis remains to be shown.

One popular form of practical therapeutics for the control of obesity is the use of so-called appetite suppressants. In a society with access to unlimited quantities of food, the problem for many is when to stop eating. The clinical response to dietary restrictions is disappointing indeed, and there is a pressing need for some method of controlling appetite that does not depend only on the patient's ability to exercise restraint at the table. The commercial possibilities for appetite suppressive drugs have not been wasted on the manufacturers, and there are now 25 or more such preparations available in this country. Most of these drugs are ephedrine derivatives. Some years ago my colleagues and I attempted to assess the value of two of these drugs in the management of obesity (Hampson et al., 1960). Dexamphetamine is widely used for this and other purposes, and it seemed a useful standard for comparison with a further drug on behalf of which at that time strong claims were being made for its efficacy as an appetite suppressant, namely phenmetrazine. Both were compared against an inert placebo made of chalk.

This clinical trial was arranged with out-patients attending for dietary advice and they were all prescribed diets of approximately 1000 kcal. daily. They were seen at intervals of one week, and were given each treatment in turn for 3 periods each of 6 successive weeks duration, making 18 weeks in all. The order of administration of the 3 drugs was randomised, so as to eliminate as far as possible bias in favour of or against a regime because it came earlier or later in the period of study. Analysis showed that both the drugs were somewhat more effective than the control tab-

lets, but that when the results were rearranged and compared, irrespective of the drug but rather between the order of the 3 periods of treatment, much more was achieved in terms of weight reduction in the first period of 6 weeks, than in either of the two succeeding.

From this has emerged the view that this group of drugs may have some little help to offer, but only as a temporary expedient. It is widely recognised that they must be regarded as drugs of addiction, and indeed our psychiatrist colleagues as well as others would be glad to see their use in the treatment of obesity restricted or abolished altogether. Anorectic drugs are never a substitute for the discipline of dieting, and the marginal benefits they have to offer seldom justify their use.

Practising doctors are constantly preoccupied with the necessity for weight reduction and the difficulties surrounding this process. Prophylaxis is the essence of good treatment, and this applies to overnutrition just as it does to so many other disorders. Although so much attention has been paid to the process of reducing weight, very little has been done to study the mechanism of gaining weight in the obese. Several years ago Dr. Passmore and his colleagues (1955) carried out energy balance studies on a group of thin young men who were overfed to capacity for a relatively brief period. In 1962 we (Passmore, Strong, Swindells and el Din, 1963) did the same for a pair of overweight young women who after a period of equilibration ate as much food as they could tolerate. In the course of 9 days overfeeding, largely with carbohydrate, they gained almost 3 kg. in weight, but in 6 days afterwards of almost complete starvation, they not only lost the 3 kg. gained, but also almost 3 kg. further as well.

When the findings in the fat young women were compared with the thin young men, remarkable differences were seen. These studies suggest that there is some substance in the frequent complaints of the obese about what they regard as a form of biological injustice and what is sceptically disregarded by their physicians, namely that when taking the same amount of food as their thinner fellows, they gain weight, while the lean remain so. For a given excess of calories, the fat girls gained weight much more dramatically than the thin men, and indeed for comparable gains of weight, the excess of calories required by the thin men was more than twice that for the girls. For a gain of 2.5 kg. in weight, 20,000

kcal. each was needed by the thin men, as compared with 10,000 and 6,500 respectively by the two fat girls.

This procedure of comparing the fat with the lean has led to studies in other aspects of metabolism as well, including steroid hormone metabolism. In recent years many reports have appeared, mainly concerned with adreno-cortical function, and usually showing that the excretion of 17-hydroxycorticosteroids was greater in the fat than in the lean. Analysis of this data commonly indicates that the higher findings recorded are associated with, and possibly accounted for, by the greater bulk of the obese patient. There is no doubt that some fat people go through a phase when their adrenocortical function is so vigorous as to create serious doubts regarding their clinical status, in the sense that they may be regarded as suffering from Cushing's syndrome.

Our own studies on this aspect of obesity were concerned with oestrogen metabolism in a group of postmenopausal patients who ranged from the extremes of being underweight to overweight (Brown and Strong, 1965). Injections of oestradiol were given, that is one of the precursors of all the oestrogen metabolites to be found in the urine. The methods of assay available at the time made it possible to study the recovery of the administered material in the form of two of the major metabolites, namely oestriol and oestrone. It was found that the heavier the individual, the greater was the recovery of administered oestrogen as as oestriol, and the less as oestrone. This has interesting potential repercussions, since the biological activity of these oestrogen metabolites varies very widely, and some of the metabolic and other abnormalities to be found in the obese might be due to factors of this type.

One further aspect of our eating habits should be mentioned. S t u n k a r d has described what he calls the "night-eating syndrome", implying that this group of obese patients eats little during the day, but in the evening and at night consumes large quantities of food. This perhaps is an extreme example of a common habit of eating little or nothing of energy value at breakfast or lunch, but then taking a large evening meal.

Hollifield and Parson (1962) have studied a comparable regimen in rats. One of two similar groups of rats was allowed free access to food at all times, while the other group was allowed to feed for two hours daily only. After a brief period when the "2 hour feeders" lost some weight, they rapidly caught up with and overtook their controls who had free and constant access to food, as is usual with laboratory rats. The different rates of gain in weight were not accounted for by differences in food intake, and other studies of fat metabolism were thought to provide a tentative explanation. So far as is known the activity of the animals was not controlled, and one possibility would seem to be that the "2 hour feeders" soon learned when it would be to their advantage to hunt for food, and that for the rest of their time they conserved their energy in rest or sleep.

Studies of the metabolism of labelled acetate by these animals showed that the "2 hour feeders" in the course of seven days increased enormously their capacity to store the acetate as adipose tissue. The suggestion is therefore that adaptation to this unusual type of feeding regimen radically altered the metabolism of the animals, so that they developed what may be described as a "storage phase" of fat metabolism.

These and many other metabolic differences that are emerging to distinguish the fat from the lean offer the prospect that out of these investigations may arise better methods of managing disordered weight control and so reduce an important source of morbidity and mortality in the better fed countries of the world.

The wonder of it is perhaps not so much that some become obese, but rather that this fate overtakes so relatively few.

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AETIOLOGICAL FACTORS IN CONGENITAL ABNORMALITIES

By ALEXANDER M. DAVIDSON, B.Sc.

I. INTRODUCTION

The problem of congenital abnormalities has been with us for many years. The surviving records of some of the oldest civilisations depict cases of congenital malformations. Achondroplasia is found in Egyptian paintings over 5,000 years old and the god Phtah revered at Memphis, the ancient capital of Egypt, is without doubt one of these cases. Club foot and cleft palate have also been detected in records and mummies of the Egyptian era.

In other ancient civilisations, abnormalities have also been recorded. Prehistoric Peruvian pottery has been found to depict hare-lip and other malformations. Greek mythology included many instances of monsters which presumably have their origin in abnormalities. However, not all references to monsters by the Greeks were confined to mythology. Aristotle describes a monstrosity as contrary to the most usual course of nature. This is probably the earliest reference to someone thinking that congenital abnormalities are due to the unusual development of a normal process.

Although painting and sculptures of abnormalities exist from some of the earliest civilisations it is not until fairly recent times that any effort has been made to determine the aetiology of such defects. In the Middle Ages the birth of a congenitally defective child was viewed with superstition and fear. Even physicians were inclined to ascribe such events to the supernatural and mystical cause. The famous French surgeon Ambroise Paré tabulated the causes of monstrosity beginning with God and ending with the Devil. This list is far from being ridiculous, and many of his ideas have a firm foundation. The causes he gives fall into three large categories—religion and superstition; environmental factors; and hereditary. Although we would generally agree that God and the Devil have no direct intervention, the other two reasons still hold.

It was not until the 18th century that some of our present day ideas about malformations had their scientific foundations. There began the collection and examination of embryos. The normal development of embryo and foetus was investigated and the deviation from normal noted. From such studies Mickel was able to show that some abnormalities are not due to random growth but persistence of some stage of normal embryonic development. It was not long before many theories arose explaining all abnormalities on this basis. This prompted

investigations into factors which could influence the development of an embryo and thus the era of experimental embryology began. Since the early experiments, work has increased in amount and in variety.

II. AETIOLOGY

The causation of congenital malformations can fall into two main groups: Intrinsic factors and Extrinsic factors. The intrinsic factors are genetically determined anomalies either due to alteration of the gene or the chromosome. The extrinsic factors include all agents which can have an effect on the normally developing child. This list includes such factors as radiation, drugs, mechanical disorders of the womb producing pressure symptoms, infections, dietary deficiencies, hormonal imbalance and environmental factors. However, although this list is impressive by its length, it is important to realise that the aetiology of most malformations is not clearly understood. Even in cases where a causal agent can be detected it is still obscure how many of these factors produce their effect.

INTRINSIC FACTORS

Genetic and Chromosomal

In the case of the chromosome there are two main types of aberrations, either anomalies of number or translocation of part of the chromosome. Probably the best known anomaly of number is trisomy 21 associated with mongalism. There is an interesting malformation of the hands in such patients — a horizontal palmar crease and characteristic finger prints are seen. This was probably the first congenital condition connected to a chromosomal defect. Other trisomy conditions have since been recognised. In trisomy 17-18 there is a flexion deformity of the fingers, mental retardation, hypoplasia of the mandible, small mouth, low set ears and ventricular septal defect. Another recognised condition is trisomy 13-15 in which polydactyly —frequently quadrilateral, mental retardation and eye defects are seen. How the extra chromosome in such cases produces these manifestations is pure conjecture.

Alterations in the gene can lead to a wide variety of conditions. Hereditary malformations of the digits are fairly common and can in some cases be traced back through many generations. Phalangeal synostosis can be traced back for fifteen generations in the family tree of the Earl of Shrewsbury. In many instances a genetic defect may not produce such a simple picture. In arachnodactyly due to a dominant gene, there is a multitude of malformations both ectodermal and mesodermal. There are long hands with spidery fingers, spinal anomalies are common, including hemivertebrae, the eyes are often affected in numerous ways and heart anomalies are common. The fact that there are multiple anomalies, some of which may occur alone, lead many people to think that such a syndrome was due, not to one gene, but multiple gene abnormalities. The present day feeling is that the gene is no observer of germ layers and that there is almost no limit to the effects that they can produce. However, it may be that with further research a syndrome with multiple defects will be traced to a single enzyme defect in a similar way to the recent elucidation of phenylketonuria. Alternately the defect may be in an organiser which would be much more difficult to trace and characterise.

EXTRINSIC FACTORS

Radiation

At the present time there are three main means whereby we can be exposed to ionizing radiation; during therapy, from environmental background and by accidents.

Radiotherapy may play an important part in the treatment of disease. As it is normally administered by competent people, the hazard from this source is considerably reduced. In many cases, however, the difference between adequate and harmful dose is small and difficult to judge. Changing the dose of radiation by as little as 10% may render the dose lethal, a point seldom considered by people not used to dealing with therapeutic agents having this fine borderline between curative and lethal doses.

The environmental radiation has always been present but recently due to such devices as diagnostic X-rays, the explosion of test nuclear bombs in the atmosphere, the development of peaceful uses of atomic energy and many other causes the background radiation has increased. This means that in his lifetime man is exposed to a higher level of whole body ionizing radiation. Besides this increase in background radiation there is an increase in the number of individuals employed in the manufacture and use of radioactive materials. The effect of such long-term low-level exposure is not known but the possibility of delayed effects appearing in later generations must be borne in mind.

The third means of exposure is due to an accident at some nuclear installation or during wartime. The effects of this vary from death to little or no detectable change. Accidental exposures of these kinds are rare and it is to be hoped that no further intentional high yield explosion will ever take place.

Radiation can produce cellular damage by different methods. It may, if strong enough, produce cell death in the intermitotic phase or in cells incapable of further division. It may delay or completely inhibit mitoses, or if mitoses takes place there may be chromosomal changes or alteration in genes. Mutations in chromosomes can be seen as visible breaks and structural rearrangement of the individual chromosomes. Gene mutations, on the other hand, are noticed only by the effect they produce. A gene is regarded as a small discreet part of a D.N.A. molecule and a mutation is caused by a change in its chemical composition or steric arrangement. Naturally occurring mutations may be the result of background radiation on the gene.

The amount of harm which a given dose of radiation will produce is impossible to estimate. If the gene is harmful, such as the one for haemophilia, then any increase in the mutation rate from normal to pathological will cause an increase in handicapped people. However, many genes are not capable of producing pathological alleles.

It is therefore necessary with regard to radiation to ensure that workers and patients receive only the minimum amount of radiation and that pregnant women receive radiation only after careful consideration.

Drug-induced

There is no doubt that drugs of various kind can produce malformations. This was brought out dramatically recently by the thalidomide disaster. It is now known that thalidomide taken any time between conception and three months is likely to produce an abnormality of the limbs. The type of malformation produced is variable. There is frequently a small haemangioma on the forehead, the bridge of the nose is depressed and small ears are not uncommon, phocomelia or seal-like limbs are usual quadrilateral and are the commonest limb deformity. However, in the limbs there may be all degrees of malformation, from complete absence of the long bones to absence of the thumbs only. Defective or absent radius with accompanying deviation of the hand is common. Single limb defects are rare although in a quadrilaterally affected child one limb may be more affected than the others. In some children mental retardation may be noticed but this is by no means common.

In discussing thalidomide it is as well to keep in mind the number of deformities it produced. Between 1960 and the end of August 1962 there were 805 live-born children with limb deformities in England and Wales. Of these 153 subsequently died leaving 652. Of this number only 244 were due to the mother having ingested thalidomide at some time during pregnancy. In Scotland the situation was a little better with only 51 of the 114 deformed babies being due to the ingestion of thalidomide.

Other drugs are also known to produce foetal malformations. Drugs which inhibit tumour growth do so in many cases because the tumour cells are divided more rapidly than the normal body cells. With this in mind it can clearly be seen that these drugs will exert some effect on the actively growing embryo. It is understandable that the embryo may experience a temporary inhibition of growth resulting in distortion. To a large extent it will depend upon time of administration and dosage of the drug whether a deformity or a stillbirth will follow. Many other types of drugs have been incriminated in congenital malformations but in many cases it is difficult to prove the relationship between the drug and the malformation produced. It is even more difficult to prove that a given drug will not produce abnormalities.

The important factor to bear in mind is that

in the majority of cases the malformations produced by drugs can be avoided. To achieve this a greater control over the prescribing of drugs linked with congenital malformations must be exercised. New drugs must be used with caution until they have been proved by time to be safe. While all species do not react in the same manner to drugs it would be advisable to test new drugs on pregnant animals of several species receiving variable doses of drugs at different stages of pregnancy. In this way some idea about the teratogenic actions of a drug may be revealed but it is by no means an absolute test.

Infections

Following the discovery of bacteria it was thought that congenital malformations were due to bacterial infection. It was known that syphilis would cause foetal death with subsequent abortion and so syphilis was named as the prime cause of malformations. However, with the introduction of therapy against syphilis and the subsequent fall in its incidence not followed by a corresponding fall in malformations investigations turned in other directions. As with so many other cases, investigators were looking for one cause of malformation. We now know that this concept is false and that bacteria and viruses do have a part to play in the aetiology of abnormalities.

It is well known that rubella in the first trimester of pregnancy may produce malformations. The mechanism whereby the rubella virus produces its lesion is unknown but it has been suggested that it is due to the localisation of the virus in the developing embryonic cells causing their death. Other theories are that the virus initiates a metabolic defect or that it constricts blood vessels producing anoxia. However, as with most conditions which have a multiplicity of theories as to aetiology little is really known as to the mode of action of the rubella virus.

Dietary Deficiencies

Although malformations can be produced in animals fed on diets lacking in some constituents these malformations are not found in humans. The only dietary factor of any proved significance is iodine. Endemic cretinism occurs in areas where endemic goitre is common. The child is born with an enlarged thyroid and shows a generalised lesion of bone, the growth of which is severely impaired. The bones are smaller and shorter than normal due to a defect in endochondral and intra-membranous ossification. An interesting feature is the presence of deaf mutism in many of the affected cases.

Hormones

Disturbances in hormones in the mother have been regarded as causes of congenital anomalies but this is not based on sound evidence. About the only defect due to this cause has been the appearance of masculinised genitalia of some female children born to mothers who received synthetic progesterones for threatened abortion.

III. SUMMARY

In this article only some of the known causes of congenital malformations are discussed. The aetiology of many conditions has still to be worked out and with further elucidation the door may be opened towards prevention of many of these crippling conditions.

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RES MEDICA

"THE OLD ORDER CHANGETH"

The Royal Medical Society will leave its present premises for temporary ones, with the hope of eventually moving into new accommodation in the projected 'Island Site' near the McEwan Hall. Women are allowed full membership. At first Private Business time is spent on issues of pre-clinical interest, instead of Society matters. At such a time it is justifiable perhaps, to speculate on the future of the Society, to conjure up visions of its future. A nightmare and a dream emerge.

The nightmare is a fleeting one. A venerable institution, some 228 years old, its quarters surrendered, parts with its library — the old dusty tomes so much a part of the society— and moves into 'temporary' premises. With no vision of its role in the student world of the 20th century, comforted by its past glories, it prefers quiet comfort as a small 'Medical Club'. It speaks with a small voice because student support is limited. The cries for help and for new premises grow weaker and weaker. They die away eventually. Nothing remains.

But the dream is insistent. The Society, leaving its premises, also leaves its lethargy behind. It is composed of students who visualise for the Society a central role in medical student life. Because of its activity and drive its temporary accommodation gives place to facilities in the Island Site which form a framework for Society activities. A Meeting Hall, a warm Library with journals and current text-books, a lounge where students can relax, drink coffee and talk, are continually in use. Erudite guest speakers learnedly address the Society, and the society members present dissertations. Private meetings are the hub of the Society, with lively, informative discussion, with films, debates, and clinical presentations. Freshers visiting for the first time are drawn into the discussion. It is a Society which combines its historic tradition of quality with vigour and enthusiasm.

One wonders whether the Society will be a dream or a nightmare.

HOUSE-JOBS

IN SEARCH OF CLARITY

The scramble for house-jobs in Edinburgh is a continuous one, spread, as it is, over the last two years of the medical course. As there is no official statement about obtaining these posts, information is handed down from year to year in a haphazard fashion. Some posts are offered early, before final year and sometimes before fifth year. On other units, housemen may be selected after finals.

The present system, if 'system' is the correct word for what occurs each year, has inherent frustrations for 'chief' and student alike. The consultant in charge of one of the less fashionable units may make his selection early to ensure that the posts are filled. But he may later meet students in senior cliniques, in clerkships and in locums who he may prefer to have

as house-men. Furthermore, the student accepting a post early may, if offered what he considers a more preferable post, turn down the earlier offer. The annoyance of the 'chief' is understandable particularly if he has refused desirable applicants because the post was filled.

Another consequence of the present system is that students who are not given jobs early automatically apply for the still vacant jobs. Hence there are long lists of applicants in the final term, often for jobs already promised.

The chief has always had, quite correctly, complete responsibility for selecting his house-men. But surely his task can be made simpler, and the students position clarified. The following suggestions may bear consideration, discussion, and, who knows, introduction.

1) A fixed final date for applications, e.g. 1st March. Students are then clear when to apply, and many 'chiefs' have had wider contact with students before final selection.

2) A date by which selections should be made, perhaps a fortnight later.

3) Successful applicants are then informed, and are required to accept or refuse within a week. Those having been offered more than one post, will accept the post of choice. Successful applicants will also immediately withdraw other applications.

4) The position would then be that a large percentage of applicants will have been offered and will have accepted posts. Posts which have not been accepted can then be offered to remaining applicants.

Such an arrangement does not increase the work of the 'chief' in selecting house-men, nor does it detract from his freedom to select his house-men. He may still 'promise' jobs if he wish. The only alteration is in the time of selection. For those who select their house-men early, the frustration of late refusals of posts is eliminated, and their choice of house-men increased. For those who select their house-men late there is little alteration. Certainly it will bring clarity to the students who, perplexed by the wide range of times of selection, wonder whether they should make early applications, before the experience of a variety of cliniques, before further clerkships and locums.

SYLLABUS

SPRING 1965

Fri. Jan. 15 ADDRESS: Profesor S. P. V. SHERLOCK, M.D., F.R.C.P. "Jaundice."

Fri. „ 22 Dissertation: R. A. CLARKE, Esq., B.Sc. " Medicine in Africa."

Fri. „ 29 Dissertation: T. BALFOUR, Esq. " Wayside Houses of Ill Repute."

Fri. Feb. 5 Dissertation: C. LOCKIE, Esq., B.Sc. "Experiences in Pharmacology."

Fri. „ 12 TALK: Dr M. K. MacDonald, M.B., Ch.B. "The Ultrastructure of the Kidney in Health and Disease."

Fri. „ 19 To be arranged.

Fri. „ 26 ADDRESS: Dr E. SAMUEL, M.D., F.R.C.S., F.F.R., F.R.C.P.E. " The Anatomy of Diagnosis."

Fri. Mar. 5 President's Valedictory Address.

Wed. „ 10 Annual Extraordinary General Meeting.

PRIVATE MEETINGS

The Private Meetings of the Society provide a varied programme of Talks, discussions, case presentations, and debates. First Private Meetings, held at 7 p.m., are orientated towards pre-clinical students, and Second Private Meetings are orientated towards the clinical student.

SOME ASPECTS
OF ABDOMINAL PAIN

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of Edinburgh; Senior Lecturer in Clinical Surgery, University of Edinburgh.

Based on a Talk given to the Society on 7th February, 1964.

INTRODUCTION

Pain is one of the many facets of our education where we learn the basic facts and theories in the early years of our medical course only to forget much of our learning by the time we are qualified and in practice. In the clinical years we tend too often to learn sites and types of pain by memory, each type associated with one certain disease: all too rarely do we stop and ask ourselves the question "Why?" and attempt to reconsider the basic theories in the light of the present evidence. It is a healthy attitude to challenge current teaching now and then in order to see how well it matches up to current practice and current evidence.

Pain is a prominent sympton in many diseases: its relief is often a perplexing problem to the doctor but paradoxically it can play a useful part in the construction of an exact diagnosis. A history which is well related by the patient and intelligently interpreted by the doctor is more important to the diagnosis and hence to the treatment than all the examinations, clinical or laboratory, which later follow. Indeed the history usually dictates the subsequent steps. Unfortunately the viscera of the body are not endowed with the same sensory precision as the skin and thus visceral pain is more difficult to describe and to locate than cutaneous pain. Progress in the understanding of pain has not been easy—not for want of interest but rather because of the difficulties concerned with any form of experimentation. It cannot be repeated too often that any theories offered must fit the facts. In recording the clinical facts of each case great care must be exercised to keep the facts quite distinct from the conclusions drawn from them — Darwin in the Descent of Man in 1889 warned us:

"False facts are highly injurious to the progress of science for they often endure long; but false views, if supported by some evidence do little harm, for everyone takes a salutary pleasure in proving their falseness."

Darwin's warning is all too often ignored and theories and deductions become taught as facts. Thus it is not uncommon to find Capp's work on the sensitivity of the peritoneum taught as an established fact rather than as a deduction; yet no less an authority than Mackenzie has claimed that the peritoneum is _not_ itself sensitive to cutting, scratching, etc. Similarly we are used to describing the pain of passage of a renal calculus down the ureter as "renal colic" and tend thereby to imply the rhythmic waxing and waning of pain in association with peristalsis such as happens in intestinal obstruction: having learned the term "renal colic" it is too easy to forget the true fact that the pain of renal calculus is not colic in that sense at all. Dr. French of this medical school has drawn our attention to this danger and a few minutes spent by the bed-side of such a patient will convince the student of the truth of this. An attack of "renal colic" will impress even the sceptic. Theories of the mechanisms of visceral pain have to be fairly broad in as much as they must explain not only the every day occurrence but also the unusual: this can be illustrated by the following example:—

A male aged 57 complained of severe aching pain in the right loin and rigors; examination revealed marked tenderness in the renal angle and the urine contained pus. A diagnosis of right pyelonephritis was confidently made by a senior physician who demonstrated to a clinique "the tenderness of the right kidney". The diagnosis remains unchallenged but the kidneys of this patient were sited deep in his pelvis and lay nowhere near his renal angles, nor his site of pain, nor his site of tenderness.

Our theories of visceral pain must explain the location of this patient's pain and tenderness in the so-called "proper" site.

VISCERAL PAIN AND TENDERNESS

Visceral pain is characterised by poor localisation, wide radiation and frequent reference to parts other than those stimulated — this was Head's original description. Afferent impulses from abdominal viscera run in the so-called sympathetic afferent nerves—these are in fact slow conduction nerve fibres which utilise the pathways of the sympathetic system to gain the spinal cord. They do not relay in sympathetic ganglia however and are not truly part of the sympathetic system: travelling such a path and sometimes passing along the sympathetic chains before entering a posterior spinal root, the fibres from one viscus may spread their entry into the spinal cord over several segments. This is one explanation of the difficulties a patient has in localising visceral pain with any accuracy since the ultimate location of pain has probably to be done on a mental map of reference learned by experience and usually conceived as relating to the dermatomes of the spinal segments.

Thus the pain of coronary thrombosis is located diffusely by the patient in the praecordium, the neck, the arm and even the hand: afferent fibres are entering the spinal cord at all these varying levels of segmental distribution and the pain is associated with these appropriate segments on reaching consciousness. In some instances pain is interpreted by the brain as originating at a considerable distance from the site of stimulation—an example of this has already been given. Such apparent errors in localisation have been designated as "referred pain". John Hunter first conceived the idea of pain reference when he observed that diseases of the liver could cause pain referred to the shoulder. Since then many theories have been advanced and many heated arguments have occurred on this subject. In 1920 Makenzie suggested that visceral afferent stimuli set up an irritable focus within the spinal cord and in turn this so disturbed the somatic secondary neurones that their threshold was lowered and thus cutaneous impulses, previously sub-threshold, now reached consciousness. Cohen (1947) made this basic reasoning more elegant by postulating that referred pain is due to the summation of impulses from both the periphery (for example the skin) and from a viscus together exceeding the threshold for pain. It should be stressed that this means that impulses from either source if strong enough, or from both sources together, can cause pain but such pain will be interpreted as located in the area of skin concerned. With this theory the reference of pain to a site no longer present (e.g. an amputated arm) can be explained.

Visceral tenderness, or pain induced by pressure is an accepted fact. Morley (1931) considered that it was due to the "sensitive parietal peritoneum" coming into contact with the causative lesion—thus in appendicitis the secondary pain and the tenderness were in the

Fig. 1

**Pain results
from irritated
parietal peritoneum**

Examiner's hand
in case of
appendicitis

MORLEY
(Sensitive parietal peritoneum)
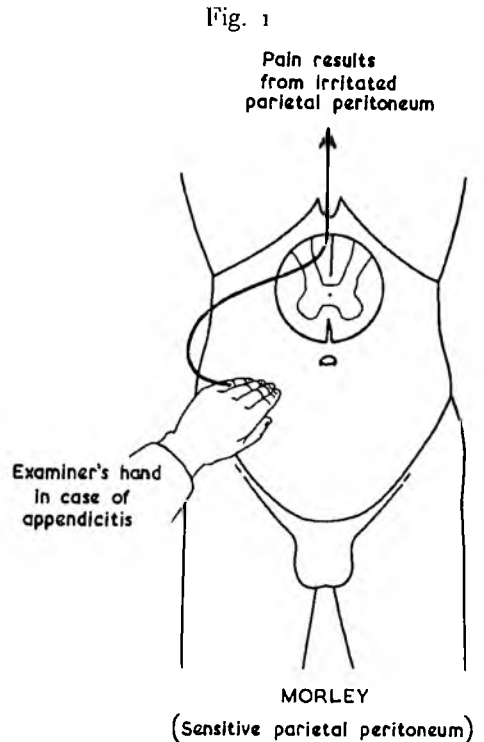
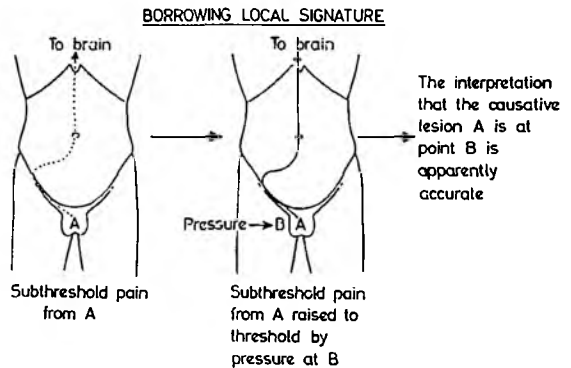right iliac fossa where the inflamed appendix lay (Fig. 1).

Kinsella (1948) has offered another theory which perhaps explains more clinical facts than does Morley's. In Kinsella's theory the pain from an organ such as the appendix travels along the sympathetic afferents and is felt in the mid-abdomen since the gut has bilateral innervation. The pain impulses probably originate in the rising tissue pressure of the inflamed organ. Movements of overlying tissues such as muscles, or pressure of an examining hand will increase the tissue pressure and aggravate the pain. The sensorium is well aware of the site of such an examining hand, etc., since the skin has also been stimulated and _consequently locates the pathology there._ This is what Kinsella has termed "borrowing local signature" (Fig. 2).
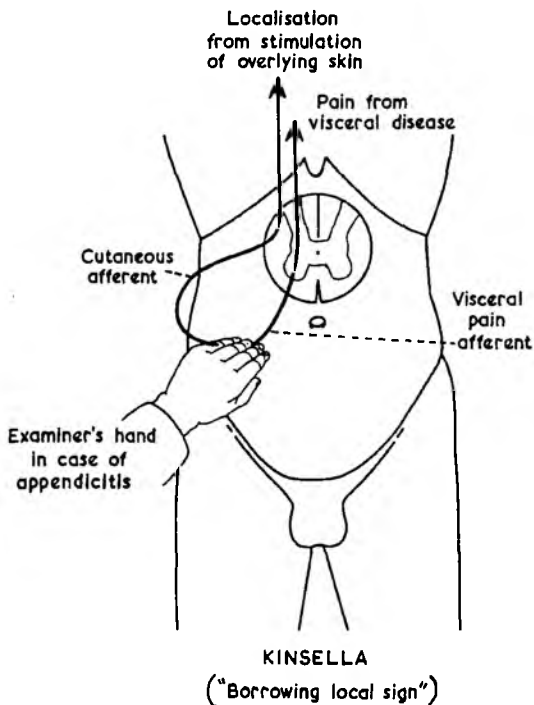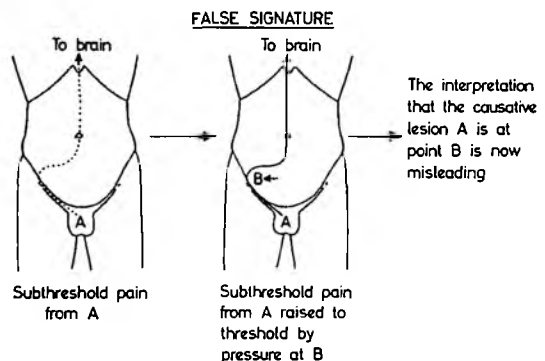
This borrowed signature may be helpful to the patient if it draws his attention to the true site of the pathology, as shown in Figure 3.

Fig. 3

BORROWING LOCAL SIGNATURE

To brain   To brain

The interpretation that the causative lesion A is at point B is apparently accurate

Pressure→B A

Subthreshold pain from A

Subthreshold pain from A raised to threshold by pressure at B

or it may be apparently misleading if the second stimulus—the examining hand—is applied in the reference area of the pain, as shown in Figure 4. It is of course the unwary clinician who is misled rather than the facts which are misleading but doctors are not immune to the desire to excuse their short-comings.

Fig. 2

Localisation from stimulation of overlying skin

Pain from visceral disease

Cutaneous afferent

Visceral pain afferent

Examiner's hand in case of appendicitis

KINSELLA
("Borrowing local sign")

Fig. 4

FALSE SIGNATURE

To brain   To brain

The interpretation that the causative lesion A is at point B is now misleading

B←

Subthreshold pain from A

Subthreshold pain from A raised to threshold by pressure at B

Brown (1949) has offered a useful rule for referred pain, stating that an organ which is displaced from its primitive embryological position subsequently refers its pain to its

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original position, e.g. diaphragmatic pain may be referred to the shoulder in C3, 4, 5 area from which myotomes the diaphragm was developed although subsequently widely separated from those segments.

CLINICAL APPLICATION OF KNOWLEDGE ILLUSTRATED BY TESTICULAR PAIN

An intelligent interest in the subject of pain must be carried over by the student from his basic science education into his clinical practice and will be amply rewarded by a better understanding of the patient's difficulties of description and localisation.

The subject of visceral pain can perhaps be illustrated better, and the current theories tested, by referring to one specific viscus. The testis is such a viscus, has its own peritoneal sac in the tunica vaginalis testis and yet is situated in an inaccessible site outside the abdomen following its descent from its primitive embryological position.

The testes develop in the same site as do the ovaries, at the brim of the true pelvis, deep to the deep inguinal rings. At this stage they acquire both their blood supply and their nervous connections which subsequently descend with the testes into the scrotum. Can there then be any good reason why a boy with a twisted testis (remember that this pathology does not involve the scrotum until a very late stage) should be expected to have pain in the scrotum while his sister with a twisted ovary has pain in the iliac fossa? It is a common misconception that pain FROM the testis is synonymous with pain IN the testis. In view of its superficial and easily accessible position one might expect acute testicular pathology to advertise its occurrence at an early stage yet a study of cases of testicular torsion reveals astonishing delays: Robb (1956) calculated the average delay between onset of symptoms and admission to hospital as 5.5 days. He also showed that in a large proportion of cases the testis is destroyed by the vascular insufficiency which occurs—of 30 patients he found only 3 who were left with a normal testis at follow-up. Since many of the patients suffering from this condition appear to have an underlying developmental defect often in the form of an extended mesorchium, and since that defect

is usually bilateral, then infertility if not eunuchism is a possible outcome.

The large proportion of testes which are irretrievably damaged by torsion before coming to operation can be explained by the diagnostic delay: but what causes the delay? A study of these cases suggests that the procrastination is occasioned by the site and nature of the earliest discomfort or pain being misinterpreted by patient and doctor alike. Nearly all current text-books still teach that patients with torsion of the testis present with pain IN the testis. But in fact the initial pain is felt in the groin or lower abdomen in keeping with Brown's law referred to above. Indeed most men have at some time experienced the sickening pain in the lower abdomen or groin which follows a blow on the scrotum.

*Evidence for the site of testicular pain:*

Three lines of evidence can be offered in support of the abdominal or groin site for testicular pain: in turn the theories of Morley, Kinsella, Mackenzie or Cohen can be tested against the clinical facts by the student interested in these problems.

i) A study of patients with spinal cord transections can be made and such patients' testicular sensation assayed with the concomitant knowledge of their sensory loss as mapped out by skin segments. Such a study suggests that when T 12 cutaneous segment is sentient, these patients have testicular sensation also but refer the pain resulting from testicular compression to the groin or to the area of the deep inguinal ring even although the skin over that area is itself insensitive.

ii) Hunter's advice of "try the experiment" can be taken. A series of volunteers had their scrotums anaesthetised by local anaesthetic. A needle was then passed through the anaesthetised skin into the testis: the volunteer felt no pain from this manoeuvre provided the needle was sharp. Through the needle the intra-testicular pressure was raised by the injection of normal saline: the volunteer remained unaware of the moment at which this occurred until the pain threshold was passed; he then recorded only his subjective pain *from* the testis (it could be relieved immediately by lowering the pressure). Such experiments have been conducted both by Brown (1949) and the author independently and invariably the pain so produced was located at the deep inguinal ring (Fig. 5) but was poorly localised, dull and sickening.

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Fig. 5

PAIN FROM EXPERIMENTALLY RAISED

TESTICULAR PRESSURE
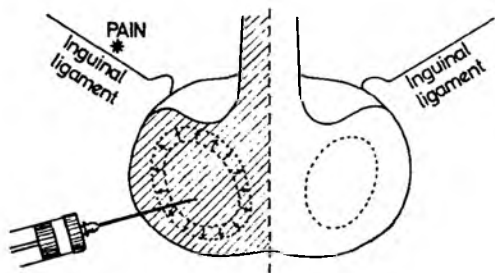
iii) The third source of evidence is to be found in the best laboratory of all—clinical practice. Thus patients with testicular pathology or vague lower abdominal pain can be studied in detail, their histories taken with patience and care, their relatives interviewed and their pathologies and clinical courses noted. Such a study again leaves little doubt that the site of the earliest discomfort or pain in a patient with testicular pathology is in the groin or lower abdomen and only later is localised to the scrotum by the patient.

Patients have been seen with a wide variety of diseases of the testis (torsion, torsion of the hydatid of Morgagni, trauma, epididymo-orchitis, tumour of testis, undescended testis, infarction of testis) and the collected evidence again led to the above conclusion as to the true site of the earliest pain.

It should however be noted that many of the patients referred to in (iii) above were unaware of the association of their vague lower abdominal pain with the "later developing" testicular lesion: so often were their medical advisers. A clinical case may be quoted to illustrate such points:—

A patient was admitted to hospital for aortography as investigation of his intermittent claudication; exactly 10 hours after the injection of dye into his aorta he summoned the house surgeon to complain of abdominal pain in the right iliac fossa. The doctor concerned could find no abnormality on examination. Fifteen hours after injection the patient again summoned the house surgeon to point out that he now had pain in his scrotum when he

touched or moved the part *but not when he lay still*. Examination of the X-ray plates showed that the injection had filled the right testicular artery completely: necrosis of the testis followed.

From the clinical evidence referred to there seems little doubt that the patient's first discomfort or pain in such cases is in the region of the deep inguinal ring: this accords with Brown's law. At a later stage in the disease process the patient is enabled to localise his lesion to the scrotum either by virtue of self-examination or by pressure of his thighs raising testicular pressure still further, but in such circumstances he has really elicited scrotal tenderness, or as Kinsella put it, he has "borrowed local signature". The lesson to be learned is that early examination of the scrotum in cases of vague lower abdominal pain can elicit local tenderness of the testis at an early stage—a stage in fact when operative intervention could save a reasonable proportion of twisted testes.

CLINICAL MISREPRESENTATIONS

In 1923 Mackenzie wrote "In all your observations keep your facts distinct from your interpretation" and this advice is all too easily forgotten. The apparent logic of expecting to find pain located accurately to the site of the stimulus is so pressing to some clinicians that it can lead to frank misrepresentation of the facts. Thus on several occasions have house surgeons recorded in the case notes expressions such as "pain in the abdomen" or "pain in the groin" when admitting the patient to the ward at a time when the diagnosis was unknown: Their better qualified but undoubtedly less exact seniors have subsequently recorded in the summary of the case (or letter to the family doctor) that the patient was admitted "with pain in the testis"—the causative lesion by this time being known to be in the testis.

It is a very easy step to manipulate the facts from the point of truth to what seems to have been the truth without there being any deliberate intent to deceive. Patients too may be confused by their apparently logical conclusions concerning their own diagnosis; the mother of one boy who lost his right testis after a torsion

reflected how unfortunate her young son had been "in first having a threatened appendicitis for three days and then going and developing this trouble with his testicle". (This boy had been observed at home for three days with abdominal pain before localising his pathology to his testis.)

SUMMARY

Pain originating in the testis in a variety of pathologies has been used to illustrate the importance of an understanding of the mechanisms and theories of abdominal pain in the early diagnosis of the lesion. The same understanding can and should be applied to any visceral pain. Perhaps the term "understanding" is too presumptious—"enquiring attitude" might be more appropriate since the details of the theories are of less importance than the attitude of mind.

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LOCALISATION

OF RENAL FUNCTION

D. I. NEWBLE, B.Sc.

Classical renal physiology as taught to the undergraduate during his medical course, regards the kidney as an entity with little attempt to relate function to the basic unit of the nephron. In most instances this is permissible as it gives a functional understanding of renal processes enabling the clinician to diagnose and treat conditions where this function is impaired, either from intrinsic or extrinsic causes. However, it is not sufficient today to regard complicated organs solely in this fashion. Thus the functions of the kidney, particularly that of 'acid-base balance,' are briefly discussed at a more fundamental level

The first major advances in the localisation of renal function stem from the classical work of A. N. Richards in the 1920's. He was the first to develop micropuncture techniques into renal physiology. He related the acidification process, in the frog, to the distal tubule. Walker et al (1946) later developed similar methods applicable to mammalian kidneys. Basically, the technique was to insert a micropipette into the renal substance and withdraw samples of the tubular fluid. The site of the puncture was marked by the injection of India ink and being accurately located by maceration and microscopic examination.

Further progress was made in 1957 when Malvin, Sullivan and Wilde described their "stop flow" analysis method. Pitts et al (1958) used this method to investigate tubular function in dogs. The ureters were catheterised and priming doses of creatinine PAH and phosphate were given. Infusions were main-

tained until stabilisation occurred. The catheters were then clamped for varying times ranging from 2 to 8 minutes. 20 to 40 one millilitre sample were collected automatically in vials fixed into a moving bar. Theoretically, clamping the ureter produces a rapid pressure build up in the tubules until the back pressure equals that of the glomerular filtration pressure. A stationary column of fluid is then in contact with the tubular epithelium which performs, in an exaggerated fashion, its normal functions. When the clamp is released, the fluid is forcibly ejected. The first samples obtained are those from the distal tubules and the later ones from the proximal tubules. The results showed that acidification, ammonia production and potassium-sodium exchange all reached peak values in the same samples, these being those from the distal tubules. Phosphate reabsorption occurred in the proximal tubule samples and was in no way related to the acidification process. Although this might appear conclusive there are many criticisms of the method. As samples were collected in air small pH changes could be missed. Also, the pelvis of the kidney acts as a mixing chamber, this effecting the later samples in particular. The method therefore provides valuable qualitative information but care must be taken in interpretation of the results.

One further technique has been used. Ulrich and Eigler (1958) managed to insert a polyethylene catheter into the collecting ducts of hamsters. They confirmed the long suspected fact that there is a large pH fall at

this site.

The first indication that these do not provide the complete answer came from Ellinger as early as 1940. He observed colour changes of an indicator passing along the tubule. In both the frog and the rat he found that acidification occurred specifically in the distal tubule only during a mild acidosis. If the urine was strongly acid then he found colour changes along the length of the nephron.

One of the most complete series of micropuncture studies was performed by Gottschalk, Lassiter and Mylle in 1960. The fluid collected was sealed in the micropipettes which also acted as microelectodes. The pH was determined by potential changes in the fluid. All their equipment was equilibrated with air containing CO_2 at 27 mm Hg. Collections were obtained from non-diuretic animals and from those in a state of osmotic diuresis, both normally and during an ammonium chloride acidosis. In all cases there was a progressive acidification along both sections of the tubule. (Fig 1.) This is conclusive proof that, in rats at least, proximal tubules can acidify urine. Biochemical analysis has shown that equal amounts of carbonic anhydrase, the enzyme necessary for hydrogen ion exchange, are present in both sites.
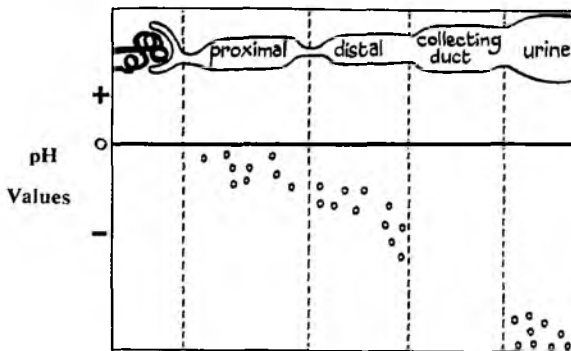

Fig. 1. Micuro-puncture study illustrating progessive acidification along the nephron. (after Gottschalk et al. 1960) The pH of tubular fluid relative to plsma pH was measured at different parts of the tubule.

Obviously this state of knowledge is far from satisfactory but it might be profitable to attempt to summarise the mechanisms proposed at this time. About 80% of the glomerular filtrate is reabsorbed in the proximal tubules under what Smith called "obligatory reabsorption". The evidence suggests that the bulk of the hydrogen ion exchange also occurs here.

The distal tubules are capable of the same processes and probably act as the fine adjustors of pH in the same way as they regulate the 'facultative reabsorption" of water. The collecting ducts can make very little contribution to overall sodium and bicarbonate reabsorption as the load presented is very small. Large pH changes could occur with a relatively low hydrogen ion secretion rate.

Having thus attempted to localise the processes in the occurring kidney the actual mode of transport of ions by the tubular cells must be discussed. The first recorded experiments on active transport in the kidney came from Wilbrandt in 1938. These he performed on Necturus which is an animal having conveniently large nephrons with long straight proximal tubules. He measured potential differences between the surface of the kidney and the lumen of the tubules using for electrodes micropipettes similar to those used by Richards. He obtained "transtubular potential" values of up to -12mV, negative inside the lumen. This he interpreted as being due to different ion permeabilities on the two sides of the cell.

Ussing et al (1951) demonstrated a potential difference across frogs' skin arising as a consequence of active transport. He defined this as ion transport against an electro-chemical gradient. Perhaps more well known are the experiments of Hodglin et al (1952) where the electrical activity of nerves was shown to arise from the passage of Na and K ions across the cell membrane. Not unnaturally, workers turned to the kidney to study these processes as it is an organ where it is relatively easy to make electrical recordings and to determine ionic concentrations without substantially altering the physiological conditions.

Solomon (1957), utilising the specialised electrodes developed in nerve and muscle studies by Ling and Gerard, observed a bimodal distribution of potentials on random insertions into the tubules of rats. During the puncture, transient higher potentials were recorded indicating that the electrodes were passing through cells with a greater negativity than the lumen. The lower range was related to the proximal and the higher to the distal tubules.

Giebisch in a much fuller investigation using the proximal tubules of Necturus found a mean value of -72mV for the peritubular membrane potential (i.e. the P.D. between the peritubular fluid and the inside of the cell) and of -20mV for the transtubular potential. By difference,
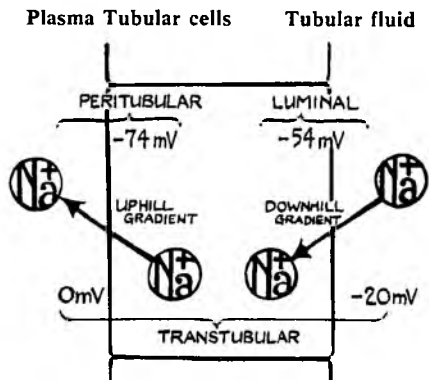
Fig. 2 Diagrammatic representation of Proximal Tubular Potentials (Values after Solomon, 1957)

Fig. 3. Diagrammatic representation of ionic transport in tubular Cells.
(a) linked with Na Pump   (a) ? K pump
(b) passive   (b) passive

the luminal membrane potential was about 52mV negative inside the cell. Reductions in these potentials were produced by oxygen lack and by mercurial diuretics which have both been shown to reduce active transport processes. (Fig. 2.)

In investigations of the transtubular potential, direct microanalysis showed no concentration gradient between the peritubular and tubular fluids for Na, H and Cl ions. The potential difference is not, therefore, maintained by ionic concentration gradients. There must be one or more active mechanisms involved. Many workers believe that Na is the only ion actively transported while the other ions follow passively down the electro-chemical gradients set up. In Necturus, at least, there is probably some active K transport. The primary process can be regarded as a shift of positive ions from the lumen leaving it at a negative potential. This is a process requiring energy.

Microanalysis also shows that the Na concentration inside the cell is less than that in the tubular fluid. As shown above, the inside of the cell is at a more negative potential than the lumen so Na ions can passively enter the cell along an electrical and a chemical concentration gradient. However the opposite is true of the peritubular border so it is logical to assume that the active mechanism is situated here. This appears to be substantiated by electronmicroscopy where the mitochondria are shown to be almost exclusively situated on this border. There is some evidence to suggest that K uptake into the cell is linked to this "sodium pump" as the concentration of K inside is greater than would be expected if only passive forces were involved. (Fig. 3.)
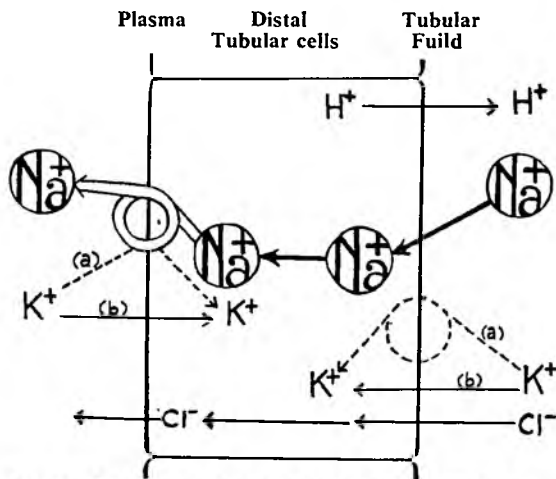
This interpretation is obviously oversimplified. Refined techniques involving single nephron perfusion, measurement of ionic fluxes utilising radioactive isotopes have all been used, but the calculations involved in these methods are complex, and cannot be adequately discussed here. It would also be unwise to attempt clear interpretations and explanations at this stage of research.

Medicine is no longer an empirical art. Soon it will be inadequate to know simply what alterations in blood and urine biochemistry indicate. The basic changes occurring at cellular and sub-cellular levels must be understood. This article illustrates the limited advances made in one small field but perhaps indicates also the trend of research in the future.

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"OBSERVATIONS ON LIPID METABOLISM"

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Based on a Dissertation presented to the Society on 25th October, 1963.

Prior to 1936, it was the custom to regard adipose tissue of an accumulation of inert lipid material, possessing little or no metabolic activity, but, in that year, this viewpoint was challenged by the work of Schoenheimer and Rittenberg. On the basis of measurements of the rate of disappearance of labelled fatty acids from the body of the mouse, these workers concluded that the half-life of the total fatty acids in this animal, under the conditions of the experiment, was of the order of three days. Since the depots constitute by far the greatest part of the body fats, it was assumed that the turnover rate observed was that characteristic of the depot fat. The acceptance of these results necessitated the immediate rejection of the long cherished idea that adipose tissue represents an inert lipid store, capable of change only during periods of fasting or of excess ingestion of food.

This "about face" in belief naturally stimulated many workers and confirmatory results appeared rapidly in the literature. Thus, Shapiro and Wertheimer evaluated the oxygen uptake of adipose tissue *in vitro* and took the elementary precaution, or so it appears now, of expressing their results in terms of the fat-free weight of the tissue in this way demonstrating that "depot fat" (so-called) ranked amongst the most active tissues in the body when judged by this criterion. In 1942, Tuerkischer and Wertheimer reported that all dietary regimens which enhance fat formation also give rise to the deposition of glycogen within the adipose tissue cells. Furthermore, these authors pointed out that this accumulation of polysaccharide is associated with high respiratory quotients, often

exceeding unity, indicating that active fat synthesis is occurring. More recently, isotopic evidence of fat synthesis in adipose tissue *in vivo* has been obtained by Fararger and Gerlach who found that the fatty acids of rat mesenteric lipid have higher specific activities than those of either liver or blood shortly after the injection of radioactive acetate or glucose.

Isolated enzymes of adipose tissue have, to date, been studied relatively little but it may be assumed, from the fact that the tissue is capable of performing such reaction sequences as those involved in respiration and fat and glycogen syntheses that many enzyme systems do occur in this tissue. There is nothing to be gained by further discussion of these systems here—suffice it to say that the main point established by the endeavours to demonstrate enzymic activities in adipose tissue is its evident marked specialisation in terms of lipid metabolism. While most of those enzymes sought can be detected in this tissue, those concerned with fat metabolism show an activity equal to or exceeding that of their counterparts in the most active tissues of the body.

For many years reports appeared sporadically in the literature of small amounts of non-esterified fatty acid (**Nefa**) which can be detected in plasma, but until the early 1950's this lipid fraction was widely regarded as an artefact of isolation. At this time, however, Gordon pointed out that certain observed "anomalies" in the electrophoretic mobility of plasma proteins may be reproduced *in vitro* by the addition of sodium oleate to plasma prior to the application of the separatory procedure. This

provided the first clue leading to the suggestion that **Nefa** might be a physiological component of the circulating lipids, but it was not until a year had elapsed that Gordon and Cherkes ascribed to this fraction an important role in the transport of fats from the depots to the tissues for oxidation. This contention is supported by several lines of evidence. First, it has been shown that **Nefa** injected into various experimental animals has a circulating half-life of the order of only two minutes, indicating its rapid removal from the blood. Second, estimates made of the arterio-venous differences in plasma **Nefa** levels across various organs have indicated that, for example, the myocardium of the fasted animal is capable of removing 0.3 MEquivalents of **Nefa** from each litre of the perfusing blood. In order to assess the physiological significance of this process, the authors performed concurrent measurements of oxygen uptake and, on the basis of the assumption that the average molecular weight of the fatty acid taken up is 275 (i.e. a mixture of fatty acids quantitatively distributed about the hypothetical C_{17} compound), they arrived at the conclusion that the quantity of **Nefa** taken up by the heart if sufficient to provide the bulk of its energy requirement under the conditions of the experiment.

The next problem requiring explanation was the mechanism by which the constancy of the arterial **Nefa** level is maintained, a problem to which we shall return later. At this moment, all that need be said is that all the tissues studied, including liver, appeared, on the basis of arterio-venous difference studies, to be active in the extraction of **Nefa** from the circulating fluid. The quest, therefore, was for a source of **Nefa** and the investigators turned to the adipose depots. They were not disappointed for it was found that samples of blood from the long saphenous vein, which may be regarded as draining the adipose tissue of the lower limb almost exclusively, showed large negative arteriovenous differences indicative of **Nefa** release.

Thus the pattern has emerged in which **Nefa** represents an important, readily available source of oxidizable material whose concentration in the blood is the resultant of its rate of removal by the tissues and the rate of its liberation from the fat depots.

We may now turn our attention to a consideration of the concept of "caloric homeostasis". As was noted earlier, the concentration of **Nefa** in the plasma is maintained at a relatively constant level, between the limits 0.5—

1 mEq per litre, despite the high rate of removal by the tissues which is observed in the post absorptive state. This implies the operation of some fairly sensitive control mechanism capable of relating the rate of liberation of **Nefa** to the somatic requirement. If we return for a moment to the work of Gordon and Cherkes in which the rate of uptake of Nefa by the myocardium was estimated, we find that their results apply only to the fasting state. In fact, Gordon proceeded in 1957 to repeat the experiments and obtained sequential blood samples for the measurement of arterio-venous **Nefa** differences before, and for some time after, the administration of 100 g. of glucose together with 0.1 unit of insulin per Kg. of body weight to human subjects. In this way he confirmed the previously obtained results and, in addition, showed that the ready availability of glucose, which may be regarded as a preferred metabolite, abolishes not only the uptake of **Nefa** by the myocardium but also its liberation by the adipose tissue. This work provides an extremely elegant example of the close correlation existing between those processes leading to the removal of fatty acids from the circulating fluids and those leading to their mobilization from the fat stores. In general, it may be said that all of those factors which increase the utilization of glucose, decrease the outflow of **Nefa** from the lipid depots. An ingenious explanation of this phenomenon will be quoted elsewhere in this dissertation but, at present, it will suffice to remark that the mobilization of fat shows marked dependence on the state of nutrition, and that pre-eminent in this regard is the status of carbohydrate metabolism.

We have seen, then, that adipose tissue appears to exert its influence on lipid metabolism by adjusting the availability of **Nefa** in accordance with somatic requirements for an oxidisable substrate. This being accepted the central issue quite clearly becomes that of the elucidation of the nature of the mechanism by which the adjustment is effected under physiological conditions. It would be logical to suppose that the process is subject to humoral and to nervous control and indeed, evidence that such is the case has been obtained by many investigators.

The first piece of evidence regarding the role of nervous activity was provided in 1922 by Goering who pointed out that excessive nerve stimulation provokes fat loss from the adipose tissue situated within the distribution of the affected nerve, whereas paralysis or nerve

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section results in a marked deposition of fat in the depots, the magnitude of which may be partially or totally masked by the associated atrophy of the somatic musculature. Then, in 1947, Clement reported that unilateral denervation of various fat bodies in the rat caused a diminution in the rate of depletion of triglyceride from the denervated side during fasting. Such observations suggest that the nervous system may exercise a tonic effect upon **Nefa** liberation from fat depots. This concept has found confirmation in the work of Havel and Gotofen (1960) who investigated the role of the sympathetic nervous system in the metabolism of free fatty acids and observed that administration of hexamethonium, a ganglion blocking agent, causes a reduction in plasma **Nefa** levels in the fasting dog. From observations such as these, it has been concluded that the sympathetic nervous system exercises a tonic influence on the adipose tissue which may provide for a continuous release of **Nefa** at a level which can be modified by insulin and other humoral agents. In addition to this, variation in the intensity of sympathetic activity itself might be reasonably expected to exert a direct effect on lipid mobilization.

Many humoral agents have been implicated in the regulation of fatty acid exchange in adipose tissue. We may begin by considering epinephrine. Administration of this hormone to fasting humans has been found consistently to give rise to very rapid and striking increases in the plasma **Nefa** content which can be attributed to an increased rate of mobilization from the fat depots (as shown by arterio-venous difference studies) (Gordon and Cherkes, 1956). In 1957, Wadström observed that 90 minutes after the injection of 0.01 mg. of epinephrine into rabbits there is a decrease in the triglyceride content of the fat depots associated with corresponding increases in the levels of glycerol, mono and di-glycerides. This evidence pointed to the conclusion that epinephrine activates lipolysis or, what amounts to the same thing, inhibits resynthesis of triglyceride in the adipose tissue. More recently, it has been shown by Gordon and Cherkes (1958) that the addition of epinephrine to surviving adipose tissue, *in vitro*, accelerates the rate at which this tissue releases **Nefa** into the surrounding medium.

Shafir et al. have pointed out two interesting facts in relation to the effect of epinephrine on lipid metabolism. In the first place they

observed that this hormone gives rise to parallel increases of **Nefa** and lipiprotein which latter plasma constituent is, in all probability, formed by the liver in response to the increased availability of fatty acids. The second, and perhaps the more intriguing, observation made by this group is that epinephrine exerts a more rapid effect upon lipid than on carbohydrate metabolism. Thus it is found that the hormone gives rise to a primary elevation of **Nefa** levels in plasma which gradually return to normal as the blood glucose rises. This observation is in agreement with the earlier results obtained by the same group in 1959 which indicated that the **Nefa** response to epinephrine can be prevented by simultaneous administration of glucose and insulin. The observation finds confirmation also in the work of Goldfen and Havel which showed that the **Nefa** response to norepinephrine, administration of which does not lead to marked hyperglycaemia, is sustained for a much longer time than that produced by epinephrine itself. The interesting fact emerging from these results is simply that, in time of stress, it is the lipid stores on which the body depends as a primary source of energy.

The second endocrine organ which exercises a profound effect upon lipid mobilization from storage sites is the anterior lobe of the pituitary. Some four hormones of pituitary origin have been shown to exert control over fatty acid metabolism; these are somatotrophin (growth hormone), thyrotrophic hormone (TSH), the corticotrophins (ACTH) and prolactin. It should be emphasised that the effects of ACTH and TSH are of peculiar interest in this connection, since, on the basis of *in vitro* studies, it is known that their action is not dependent upon the presence of their "target organs", though, in the whole animal, the presence of these organs will modify the lipid response observed.

The evidence so far to hand suggests that all four hormones influence lipid metabolism in essentially the same way: somatotrophin, however, by a sort of historical accident, has been studied most intensely and so the effects of this hormone will be considered at greater length than those of the other three.

In 1944, Stetton and Salcedo, injected anterior pituitary extract into mice, a procedure known to give rise to a condition of "fatty liver": they discovered by means of prior deuterium labelling that the excess hepatic lipid had been transported to that organ from

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the adipose storage depots.

The problems involved in the isolation of pure and homogeneous preparations of the various pituitary principles made further progress in this field difficult and even today, render interpretation a matter open to doubt. However, in 1953, Greenbaum and McLean reported that treatment of rats with "purified" somatotrophin caused a very rapid increase in hepatic triglyceride content. In view of the fact that the hormone is known to increase the rate of fatty acid oxidation in the liver, and bearing in mind the results of Stetton and Salcedo above, it seems apparent that the accumulation of lipid material in the liver under these circumstances must result from an increased rate of transport of fatty acids to this organ from the depot fat. That somatotrophin can increase the rate of mobilization of **Nefa** from adipose tissue is further suggested by the finding that the plasma **Nefa** level of fasting dogs, already high, may be readily increased two-fold by the injection of "purified" bovine somatotrophin.

The *in vivo* evidence of a fat mobilizing action of somatotrophin is thus fairly clear cut, but unfortunately it has so far proved impossible to demonstrate this activity of the hormone *in vitro*. In 1958, however, White and Lugel in experiments with ACTH showed that a) corticotrophins are more active than somatotrophin in promoting fatty acid liberation *in vivo* and b) that they also display a powerful effect in the case of adipose tissue *in vitro*. On the basis of these observations, White and Lugel proposed the possibility, which still awaits experimental verification, that somatotrophin may be inactive in itself but that, in the intact animal, it may be metabolised to a product which is capable of promoting fatty acid liberation from the fat depots — the analogy here to the case of L-thyroxine is so obvious that no further comment is required.

The two remaining hormones, TSH and prolactin, are not so well defined as regards their action on lipid metabolism. For example, in vitro experiments have indicated that TSH is capable of increasing the rate of **Nefa** release from adipose tissue but only when present in unphysiologically high concentrations. The state of our knowledge concerning the action of prolactin on fatty acid metabolism is equally unsatisfactory. Reiss (1947) maintains that injection of this hormone leads to well marked depletion of the fat stores, but, as in the case of somatotrophin, no *in vitro activity* can be

demonstrated. On purely teleological grounds, Reiss proceeded to argue that it is logical to expect prolactin to exercise a fat mobilising effect, especially in view of the fact that Shaw and Petersen (1938) have claimed, on the basis of A/V lipid differences across the lactating udder, that more than enough circulating lipid, in what form they do not say, is abstracted from the blood by this organ, to account for the entire lipid content of the milk. This effect of prolactin was also claimed on the basis of Houssay's observation that somatotrophin and the corticotrophins can, at least in part, replace prolactin in the maintenance of lactation in the hypophysectomised animal. A warning must be given at this point concerning the validity of such "round about" arguments however, and the whole status of the reliability of observations based upon work with so called "pure" anterior pituitary principles must be examined critically before acceptance.

We may now pass on to a consideration of insulin. Both the concentration and turnover of **Nefa** in blood are strikingly influenced by this hormone. In the normal fasting animal and in the diabetic animal, the circulating **Nefa** level is decidedly increased and indeed, in severe ketotic diabetes the molar ratio of fatty acid to serum albumin may exceed seven, which is the maximum number of fatty acid molecules which can be tightly bound by one molecule of serum albumin, the normal value being rather less than one (Goodman and Gordon, 1958).

In 1958 Dole observed that the administration of insulin causes a marked fall in the plasma **Nefa** level of normal individuals. As in the case of epinephrine considered above, the action of insulin is of particular interest in that this hormone has been shown (Dole 1958) to exercise an effect more rapidly on circulating lipid than on blood glucose. Once again, this may be regarded as a reflection of the importance of lipid metabolism in the living animal.

In addition to the *in vivo* findings outlined earlier, Cherkes and Gordon, in 1958, measured the rate of release of **Nefa** by epididymal fat bodies obtained from fasting rats, when these adipose tissue fragments were incubated in a medium containing bovine serum albumin as an acceptor of **Nefa**. In the absence of the hormone it was found that the tissue release 1.57 μm of fatty acid per gram per hour while, with the addition of physiological concentra-

tion of insulin a net uptake of Nefa from the medium was observed, amounting to 1.03 um per gram per hour. In other words the tissue which was releasing Nefa, on the addition of insulin, was persuaded to take up Nefa from the environment.

Other hormones have been reported to modify the metabolic activity of adipose tissue but their effects remain, in general, poorly understood and in the interests of brevity they will not be discussed here.

We have seen, then, some of the ways in which the uptake and liberation of fatty acids by adipose tissue may be controlled in vivo, but two very fundamental questions now present themselves. Firstly, what is the nature of the stimulus which causes the control mechanism to come into play and secondly, how is the neuro/humoral information translated into terms of biochemical process? To neither of these questions, particularly the latter, can definitive answers be given at this time but in what follows, some attempt will be made to clarify the situation insofar as it is possible, presently, to do so.

If we consider the normal physiological situation obtaining in an organism, then it is clear that the effect of somatotrophin on lipid metabolism, in the normal adult, may be assumed to be more or less negligible, though it may be significant in the young animal in which the provision of adequate amounts of oxidisiable substrate to the growing tissue is mandatory. In any event, it seems more likely than not that any physiological effect attributable to somatotrophin will be tonic in nature and not subject to rapid or marked fluctuation. On the other hand, all of the other components of the control mechanism are capable of dynamic variation dependent on tissue requirements from moment to moment. Thus, the mobilisation of **Nefa** in response to sympathetic nervous stimulation and to the release of epinephrine by the adrenal medulla is a biochemical reflection of the sensitivity of the nervous system to various types of stress, and is mediated by the activity of the higher nerve centres. Insulin, which strongly inhibits liberation of **Nefa** from depot fat and, as we have seen, may actually promote fatty acid uptake by adipose tissue, is liberated from the pancreas in response to the stimulus of high blood sugar levels acting directly upon the pancreatic cells. As I have said before, this provides an example of the close correlation existing between carbohydrate and lipid metabolism and explains the observed dependence of plasma **Nefa** levels on the nutritional state of the animal. Thus, a fasting animal may be expected to have a low blood glucose level associated with a high level of circulating **Nefa** but if an alimentary hyperglycaemia is established, the resulting increase in the level of circulating insulin may be held to explain the rapid fall in plasma **Nefa** which is observed in such a situation.

The mechanism by which this final control is actually mediated is rather more obscure. Throughout this article, reference has been made to the lipolytic activity of adipose tissue. The implication has been that the various components of the neuro-humoral control system modify the activity of tissue lipases. Clearly, however, an exactly parallel situation would arise if control was exercised by modifications in the rate of synthesis of triglyceride within the adipose tissue cells.

Let us examine these possibilities. First, the lipase hypothesis. Korn and Quigley found in 1957 that the only lipase activity demonstrable in many types of adipose tissue was that due to heparin activated "lipoprotein lipase". For this reason, a great, and perhaps disproportionate, number of investigators have studied the behaviour of this enzyme in relation to fat mobilization and deposition. Typical of this field of endeavour, is the work of Hollenberg (1959) who reported that the addition of glucose and insulin to adipose tissue from fasting animals, restores the capacity of the tissue, in vitro, to liberate "lipoprotein lipase" in response to heparin. From this he concluded that the enzyme may be concerned in the accumulation of fat in depots, possibly by influencing the rate of incorporation of lipoprotein fatty acids into adipose tissue cells. Many further studies have been undertaken and, by and large, all implicate lipoprotein lipase in the uptake of fat, in the form of **Nefa**, by the depots.

What then of **Nefa** release: in this case the substrate is rather different—not lipoprotein as in plasma, but more or less pure neutral fat (triglyceride) a fact that appears to rule lipoprotein lipase activity out of court since the activity of the enzyme toward pure triglyceride is vanishingly small. We must turn, then, to consideration of the second hypothesis, that dealing with rates of reesterification.

In 1960, Wood et al. pointed out that in rat epididymal fat tissue, glucose carbon is incorporated into the glycerol moeity of triglyceride at a rate many times greater than the

carbon of glycerol itself: they went on to demonstrate that adipose tissue homogenates require. L-α-glycero-phosphate or one of its phosphorylated precursors for optimum esterification of carbon labelled palmitate, glycerol itself being inactive in this system. If this is equally true of intact adipose tissue, then esterification of **Nefa** should be limited by the rate of formation of L-α-glycero-phosphate from glucose via di-hydroxy-acetone-phosphate.

Now it is known that the triglyceride of adipose tissue undergoes constant hydrolysis and re - esterification within the tissue: by what mechanism the hydrolysis is effected is not understood. However, it must be assumed on this evidence that, in the steady state condition, where there is no net uptake or release of **Nefa**, the liberated fatty acids are rapidly re-esterified. This re-esterification requires the presence of a supply of l-α-glycero-phosphate obtained by the metabolism of glucose via the Embden-Meyerhof pathway. The equilibrium situation between triglyceride and **Nefa** within the cells is quite obviously dependant upon a ready supply of glucose. During periods of hypoglycaemia, the **Nefa** of the adipose tissue might be expected to rise and since intracellular and extracellular **Nefa** are in a free translocation relationship this will lead to their liberation into the blood; conversely, after glucose and insulin administration the enhanced respiratory activity of the adipose tissue cells will ensure a plentiful supply of dihydroxy acetone phosphate and therefore of L.-α-glycero-phosphate so that the fatty acid level of the circulating fluid will diminish as **Nefa** is withdrawn to be esterified within the cells.

This hypothesis has been found to accord well with experimental data in which the percentage of glucose carbon incorporated into the glycerol moiety of neutral fat has been estimated under varying conditions of availability of glucose. It provides an elegant example of the indirect way in which hormonal substances may modify cell metabolism since the action of insulin on fatty acid mobilization appears in this way to be explicable in terms of a primary action of the hormone, notably that of influencing the translocation of glucose across cell membranes. Attractive though the hypothesis may be, however, a note of caution must be sounded—the energy transformations and relationships in systems such as this remain obscure, complicated as they are by the very peculiar solubility properties of the participating lipids and lipoproteins and estimations of equilibrium constants for such systems have not, so far, been attempted.

In this article a very few of the advances which have been made towards the understanding of adipose tissue and its role in lipid metabolism have been discussed. We have considered the recognition, some thirty years ago, of the fat depots as dynamic entities, the discovery of the significance of **Nefa** in metabolism and the possible means by which the control of lipid uptake and release by adipose tissue may be affected under physiological conditions.

What has emerged is still a far from coherent story and we can only wait, perhaps for a further quarter of a century in the hope that the final word may yet be spoken.

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Book Reviews

CLINICAL EXAMINATION. Edited by John Macleod. E. & S. Livingstone Ltd. 1964. First edition. Pp. 513. Price 35s.

The aim of this book is to give an account of the procedures carried out by a doctor examining a patient at the bedside or in the consulting room. It is, in effect, a book of the clinical methods of some of the consultants of the Edinburgh Medical School, and so it will naturally be read with interest by both undergraduates and postgraduates. It is impossible to learn clinical methods from a text-book—these can only be learnt by practical experience. But it is stimulating to read the techniques practiced by those with so much experience. This book will be a most valuable guide for those starting their clinical studies, and is a marked improvement over the other books on clinical methods at present available. The book is well conceived, and attractively set out so that it can be read easily. Many books on this topic fail because they are not written in an interesting manner—this is a book which looks interesting. The only criticism to be made is that 500 pages make a rather lengthy book, which should be read at a time in the undergraduate career when several subjects are making demands on time. The illustrations are good, but there are not enough —more pictures and fewer words, would increase the value of this book, which is quite likely to become very popular.

R.R.S.H.

TECHNIQUES IN CHEMICAL PATHOLOGY, by G. A. Cheyne. 397 pages. Price 42/-. Published by Blackwell Scientific Publications, Oxford.

Mr Cheyne, in the Preface, states that 'this book is aimed at the trained technician in the medical laboratory . . . is intended to guide him through the examination of the Institute of Medical Laboratory Technology . . .'. The aim is true, but the relative absence of the diagnostic significance of the various tests makes it evident that if the medical student was to be considered as a possible target, then it would be in a less important, peripheral, position. Consequently such a book is not one which can be recommended to the majority of the readers of this Journal.

B.H.

THE PRINCIPLES AND PRACTICE OF MEDICINE. Edited by Sir Stanley Davidson. E. & S. Livingstone Ltd. 1964. Seventh Edition. Pp. 1260. Price 37s. 6d.

Since it first appeared in 1952, Davidson's Medicine has been produced every year, either as a reprint or as a new edition. Such a record says more for the quality of the book than can any review. To sell 200,000 copies of any textbook in a period of eleven years is indeed a remarkable achievement!

The new edition is longer by 156 pages, but the increase in price is only slight. Each chapter has been revised and brought up to date, and the layout is rather different. There can be no doubt of the value of this clear, authoritative, and up to date book.

TROPICAL DISEASE. Supplement to The Principles and Practice of Medicine. By Sir Alexander Biggam and Frederick J. Wright. E. & S. Livingstone Ltd. 1964.

The appearance of this supplement does not mean that the old section on tropical diseases has been dropped from the main book; these tropical diseases which are of interest to the doctor in a temperate climate are still described in the main work. This supplement concerns diseases which are common or important actually in the tropics, and so is of main interest to those who work or live abroad.

R.R.S.H.

LECTURE NOTES ON PSYCHOLOGICAL MEDICINE. By T. Ferguson Rodger and I. M. Ingram, G. C. Timbury, R. M. Mowbray. E. & S. Livingstone Ltd., 1964. Second edition. Pp. 108. Price 7s. 6d.

The first edition of this booklet was published in 1962, and this second edition is substantially the same, and at the same price. These paperbacks of Livingstone's are very good value. Not intended as a text, this booklet is a very useful study aid. It can be read very rapidly and provides a good framework of classification on which further knowledge can be hung. Many students find psychological medicine a confusing subject to learn, because they do not have a sound idea of the layout of information. Familiarity with this book in the early stages of the course should prove of great help from this point of view.

A convenient glossary has been added to this edition, and this also is of great help to the beginner.

R.R.S.H.

JANUS IN THE DOORWAY, by Douglas Guthrie.
Pitman Medical Publishing Co. Ltd. Price 50/-.

This book consists of a selection of essays on various aspects of medical history. The essays, which are grouped in six sections each with a central theme, range in subject matter from 'The Search for a Philosophy of Medicine' and 'On Writing a History of Medicine', 'The Medical and Scientific Exploits of King James IV' and 'Coryats' Crudites—a Continental Tour of 1608' The second mentioned essay contains a valuable item—a paragraph devoted to the place and purpose of the book review!

We are introduced to the place of medical history in medical education and our appreciation of this view is increased as we become acquainted with various aspects of medical progress throughout the ages. The men behind a few of the great names next attracts our attention. The last essay in the collection would, perhaps, indicate that the most important factor for success in medicine is the choice of our parents.

Dr Guthrie in this book provides us with additional evidence of his ability to write on a technical subject in a manner which not only provides information but is a pleasure to read. It is this second quality which will ensure a wider interest among general readers.

J.P.

THE BIOCHEMICAL APPROACH TO LIFE, by F. R. Jevons. Pages 182. Price 28/-. Published by George Allen & Unwin Ltd. (London), 1964.

"To give conceptual coherence to the individual topics treated . . . to build up a rationale of the biochemical approach. From isolated molecules and events on the molecular scale, typified by proteins and single enzyme reactions . . . to their collaboration and organisation above the molecular level in sub-cellular particles". Such is the target which Dr. Jevons book has its sights levelled, and, after nine chapters of easy logical projection of biochemical concepts, may be said to have been hit squarely.

This year marks the beginning of new concepts in the teaching of pre-clinical students. with a greater emphasis being placed upon the scientific aspects of pre-clinical medicine. A book such as this will make the initiation rites of the novice to the new course more pleasurable and intellectually rewarding by awakening his interest in the fundamental problems of living organisms that have been solved and those that are still unsolved.

B.H.

A SYNOPSIS OF CARDIOLOGY, by D. Weitzman. John Wright & Sons Ltd., Bristol. 1964. 30/-.

This 'Synopsis' falls between two stools—the sophisticated discussion of the cardiologist and the humbler needs of the student. In 200 pages of fairly small type, 'cardiology' is presented in a clear-cut and factual manner. It is a masterpiece of classification and sub-classification. The reader may be equipped to manage the cardiological problem, perhaps better equipped to pass his examinations, but not inspired, nor enthused by this volume. A dull book, its greatest value is perhaps in clarifying ill-digested knowledge. a book for revision, but not learning from. Thus it is not a book for the newcomer. Nor is it discursive enough for the specialist. The 'Synopsis' may find a place in the shelves of the graduate who, while not a cardiologist, may wish rapidly to remind—or acquaint—himself of current ideas in this very important field.

D.L.W.D.

A SHORT HISTORY OF CHALMERS HOSPITAL, by W. N. Boog Watson. E. & S. Livingstone Ltd., 1964. 2/6.

The history of a small Edinburgh hospital is unlikely to have much sales appeal outside Edinburgh, and even that within Edinburgh may be small. But then the purpose of the book, presumably, is not for financial gain, but to mark the centenary of this small, rather plain hospital.

This book, unlike some other 'short' histories lives up to its name. Its twenty-six pages are set out in large clear type, well-laid out. Thus it is rapidly read, entertaining and informative for 15 minutes or so. The book is about the right length, any more would pall, any less would be inadequate. Constructed with the bequest of a successful city plumber, George Chalmers, as a 'New Infirmary or Sick and Hurt Hospital', the hospital has served Edinburgh for a 100 years. Beset with financial difficulties, the hospital gradually increased in size and facilities. One learns. for example, that the new nurses quarters of 1887 was placed between the wine-cellar and the mortuary. Present-day nurses might object to the latter.

The over-all impression of the book is that the hospital has been a labour of love for many nameless people. Much time and effort has gone to maintain this small personal hospital. Such devotion is perhaps salutory in an era of mammoth hospitals and government spending.

D.L.W.D.

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