BRITISH MEDICAL JOURNAL

LONDON: SATURDAY, NOVEMBER 9th, 1935

OBESITY: AETIOLOGY AND METABOLISM*

BY

C. G. LAMBIE, M.C., M.D., F.R.C.P.ED., F.R.S.ED.

PROFESSOR OF MEDICINE, UNIVERSITY OF SYDNEY; HONORARY PHYSICIAN, ROYAL PRINCE ALFRED HOSPITAL, SYDNEY;
HONORARY CONSULTING PHYSICIAN, PRINCE HENRY HOSPITAL, SYDNEY

[ABRIDGED]

By obesity is meant an excessive accumulation of depot fat in the storage areas of the body. What constitutes excess will depend upon the point of view. The physician is called upon to regard obesity as a disfigurement, as a disease, or as a "sign." The aesthetic criteria of obesity may be determined by individual taste, or even by the dictates of fashion, but there comes a point at which the deposition of fat impairs functional activity and gives rise to symptoms, so that a person may be said to be too fat if the adiposity results in distress or discomfort of any kind, impairs the sense of well-being, or diminishes the capacity to enjoy life. Ultimately, by embarrassing the heart and respiration and diminishing the resistance to disease it may be a menace to life itself. Even where it does not itself produce any deleterious results, obesity may be a feature of various disorders, some of which may shorten life. The prognosis will depend upon the disease with which the obesity is associated.

The correlation between obesity and the expectation of life is provided by insurance tables which indicate that, when a very large number of individuals taken at random are examined, the expectation of life is diminished among those whose weight exceeds by a certain percentage the mean of those individuals of the same height, age, and sex who have passed as first-class lives. It may be doubted, however, whether it is justifiable to assume that weight should increase with increasing age, as the insurance tables indicate.

The tables and formulae which have been constructed furnish a standard of normality rather than a criterion of disease, but a more accurate measure of normality might be obtained by selecting groups of individuals according to body build, instead of measuring a large number of individuals taken at random. If this were done many persons would appear less abnormal than when referred to ordinary standards. The "correct" weight for an individual should in some degree be related to the physical type to which he belongs. If this were more widely realized many people would avoid ill-health and privation through ill-advised attempts to make their bodily configuration conform to some general standard, whether derived from ideal weight formulae or prescribed by fashion.

The Sources of Fat

The depot fat of the body may be derived from all three proximate principles of food. Fat is first broken down in the intestine into fatty acids, which form soaps, and glycerol, but in the process of absorption through the intestinal wall these are again synthesized into fat. Fat in food, however, is not the only or chief source of

fat of the tissues. Carbohydrate, which is readily convertible into fat, and furnishes about two-thirds of the energy of an ordinary mixed diet, is probably the main source of body fat.

Protein may likewise be a source of body fat in certain conditions, though it is doubtful to what extent this process occurs normally. Probably when fat formation from protein occurs it is indirectly through the conversion of the glucogenic amino-acids into carbohydrate, which in turn is converted into fat. It may be that in the normal organism triose formed in the course of intermediary metabolism from three carbon atom glucogenic amino-acids does not readily condense directly to form glucose, but is either rapidly oxidized or converted into glycogen. In these circumstances it is only indirectly through glycogen that protein would form glucose and fatty acid. A reciprocal relationship appears to exist between glycogen and fat deposition in the organism. In general, conditions which lead to a deposition of glycogen in the liver also lead to an increased deposition of fat in the fat depots and a simultaneous diminution in liver fat. Conversely, those conditions which cause a fall in liver glycogen also tend to the mobilization of fat in the fat depots and an increase of liver fat.

Before depot fat is mobilized it is probably broken down into fatty acid and glycerol, to be again resynthesized into neutral fat in the blood, but little is known of the mechanism of this process. The exact part—probably an important one—played by the liver in fat metabolism is uncertain, and some doubt has lately been cast upon the hypothesis that it is concerned with converting the mobilized fat into a more readily oxidizable form, as by the introduction of double linkages into the fatty acid molecule or the building up of fatty acid molecules into complex phospholipides such as lecithin.

By the law of conservation of energy, if more energy is taken into the body than is consumed the excess foodstuff must be stored, and as the capacity of the body to store protein and carbohydrate is limited the excess is chiefly stored in the form of fat. Owing to the high fuel value of fat, energy can be stored in smaller bulk in this form than in any other. Conversely, if the consumption of energy by the body is greater than the amount supplied in the food, the body draws upon its stores of energy to make good the deficiency. The carbohydrate stores are most readily available, but, having a limited capacity, are quickly depleted, after which the depot fat is drawn upon, and, finally, the body protein tends to break down. It is reasonable to suppose that obesity would result whenever there was long-continued excess of intake over output of energy, but the question needs close examination.

* Read in opening a discussion in the Section of Medicine at the Annual Meeting of the British Medical Association, Melbourne, 1935.

Energy Requirements of the Body

The energy requirement of the body is the amount of energy necessary to cover the basal metabolism, bodily activity, and the specific dynamic action of food. The basal metabolism is the amount of energy consumed by the organism when at complete rest and in the post-absorptive condition—that is, at least fourteen hours after the last meal. It is proportional to body surface, not to body weight; therefore the latter is not a reliable guide to caloric requirements, especially in very thin or very obese persons. To double the weight, for example, would not be to double the body surface or the basal metabolism. As for the energy required for bodily activity, a rough approximation to the number of calories to be allowed might be obtained by taking the average starvation metabolism for a person engaged in a certain kind of activity and subtracting from that value the figure for basal metabolism.

The specific dynamic action is the term used to describe the stimulating action of food upon metabolism. It is due to a drug-like effect upon cellular activity exerted by certain chemical substances formed in the intermediary metabolic process. Protein, which exhibits this action in the highest degree, causes a rise in metabolism equivalent to 17 per cent. of the caloric value of the food, and in the case of carbohydrate the rise is 9 per cent., and of fat, $2\frac{1}{2}$ per cent.

In rough summary it may be said that the total daily caloric requirements for an individual of 70 kg. weight, 170 cm. height, 24 years of age, and doing light work, would be distributed as follows:

Basal metabolism	...	...	1,706	calories
Activity	...	...	534	"
Specific dynamic action	...	...	285	"
Total	...	...	2,525	"

This amounts to approximately 36 calories per kg. for twenty-four hours—the amount of energy in the food required for caloric equilibrium.

To strike an energy "balance sheet," the only item on the "income" side is food. The intake of food in most animal species is regulated by the proper correlation between appetite and physiological need, but in the human subject this correlation is apt to be upset by the numerous social and other inducements to excessive consumption. The tendency to routine in human society also leads to the persistence of eating habits once acquired, and while such habits may have been physiological at one period of life, they may cease to be so with altered activity, particularly with advancing years. It is not to be supposed, however, that the consumption of large quantities of food by obese persons is always to be attributed to such causes. In some cases it may be a response to a physiological need, especially in cases with a high carbohydrate tolerance in which excessive hunger results from hypoglycaemia, often accompanied by a specific craving for carbohydrate. Carbohydrate is cheaper than either protein or fat, more appetizing than the latter, and can be given in the concentrated form of saccharose or glucose, with the additional property of sweetness to render it tempting. Mechanical work can be performed more efficiently upon it than upon either protein or fat, with consequent saving of calories.

Food intake is by far the most important single factor capable of disturbing the energy balance. Many obese persons claim to be small eaters; it is a claim always to be accepted with caution, but undoubtedly many obese persons do maintain their weight on diets well below the average, and rapidly put on weight on diets which fail to cause increased fat deposition in other persons.

Expenditure Side of the Energy "Balance Sheet"

On the debit side of the "balance sheet" the factor of greatest magnitude is the basal metabolism. It might, therefore, be anticipated that changes in the basal metabolism would be of great significance, but actual observation shows that while in a certain percentage of cases the basal metabolism is lowered, in the majority it is normal, and in a small number of obese persons actually above the normal range. The finding of even a normal basal metabolism in very obese individuals points to an actual increase in the metabolism of the active tissues, since a large portion of the mass of the body is made up of comparatively inert fatty tissue. The presence of obesity, therefore, is compatible with lowered, normal, or increased basal metabolism, and conversely a basal metabolic rate well below the normal may be encountered in persons who are not obese.

Various factors influence the metabolic rate at rest. Among these are drugs, such as thyroid and dinitrophenol, and also the toxins of disease, endogenous and exogenous. The metabolic rate is influenced by emotion, especially worry, and in these circumstances weight may be lost. Since absence of emotion saves calories it might be expected that phlegmatic persons would be more prone to obesity. Contrary to popular impression, the majority of obese individuals consider themselves excitable rather than placid; but this excitability may be cortical rather than vegetative in origin. Exposure to external cold leads reflexly to increased metabolism and heat production to compensate for the heat withdrawn from the body, but the role of climate is made less important as a factor influencing the metabolic rate at rest by the wearing of clothing and the use of artificial heating, the effect of which is to prevent any great change in the immediate environment of the body.

There is no evidence that obesity is commoner in warm than in cold or very hot climates, nor that the wearing of excessive clothing is commoner among obese persons. That changes in external temperature are not without influence, in spite of clothing, is suggested by the fact that persons of fixed habits in regard to food and exercise tend to become lighter in winter than in summer. The heat mechanism is disordered in obesity, heat loss by radiation being diminished, though this is compensated to some extent by increased loss of evaporation (excessive sweating). Finally, among the factors influencing metabolic rate at rest may be placed affections of the circulatory and respiratory organs, in which increased work performed by the muscles of respiration or by the heart itself may lead to a definite increase in energy consumption, sometimes amounting to about 50 per cent. of the basal metabolism.

Exercise

The energy supplied in food may be consumed in mechanical work, but compared with that required in metabolism the amount of food converted into mechanical work constitutes a relatively small proportion of total energy consumption. In the example quoted above, for a man weighing 70 kg. and doing light work, it would be only a little over one-third of the basal metabolism. The energy required for work only approximates to that for the basal metabolism in individuals engaged on labour of a very heavy kind. It has been found experimentally that an individual walking at three miles an hour along a level road uses 0.0005 calorie per horizontal kilogram-metre, so that a man weighing 70 kg. would in an hour's walk covering two and a half miles require only 140 calories, or approximately the amount of energy contained in a slice of bread.

There is no evidence that the mechanical efficiency of the body is greater in the obese than in the normal. In cases of marked obesity the mechanical efficiency is actually decreased. These facts indicate that in the treatment of obesity it is much easier to produce a negative caloric balance by reducing the food intake than by increasing the amount of exercise. Apart from this, there may be disadvantages in prescribing exercise during a reduction cure, owing to the stimulation of appetite, and, of course, strenuous exercise is definitely contraindicated when there is circulatory embarrassment.

Leaving out of account the basal metabolism, which is usually normal in obesity, exercise comes next to food intake in order of magnitude and variability among the factors capable of disturbing the energy balance. Obesity is commoner among persons of sluggish habits and sedentary occupation. Many persons date their obesity from a period of enforced rest, such as an illness or pregnancy, and the greater incidence of obesity in the female sex may be partly attributable to these factors. On the other hand, a great many obese people are very active in their habits; inactivity is often only a late effect of obesity. The energy consumed as a result of specific dynamic action of food constitutes a smaller fraction of the total energy involved than that represented by any of the factors hitherto considered. The evidence with regard to any alteration in such action in obesity is at present unsatisfactory, but, such as it is, it seems to point to the action being diminished in many cases.

Over-nutrition and "Luxus" Consumption

According to the principle enunciated by Pflüger, energy consumption is determined, not by the supply of energy, but by the demands of the tissues, any excess of intake over requirements being immediately stored, chiefly as fat. If this were true, any continued, even though slight, excess of intake over requirement would eventually result in obesity. It is a matter of common observation, however, that there are people who are big eaters and who, in spite of a sedentary life, fail to increase in weight, while others who take only a fraction of the amount of food and lead a more active life become fatter. This suggests that the problem of obesity is not just one of adjustment of the energy balance in terms of the estimated requirements. Failure to lose weight on diets much below the estimated requirements or even on a basal caloric intake without complete rest is usually to be explained by water retention, lowered metabolism, or a lack of correspondence between estimated and actual energy requirements. Water retention may result from starvation, but in some cases of obesity it is so marked as to suggest some involvement of the neuro-hypophyseal mechanism regulating water metabolism. Lack of thyroid secretion is also conducive to water retention.

It goes without saying that if the energy intake is less than the energy consumption there will be a loss of energy-yielding tissue. In the presence of a negative energy balance every individual, obese or otherwise, will lose tissue substance. The fundamental problem in obesity is not so much what occurs when less food than necessary to meet the energy requirements is ingested, but what happens to the food taken in excess of the caloric requirements. The body may deal with the excess by limitation of absorption, elimination, increased mechanical work, combustion ("luxus" or excess consumption), or storage. There is no evidence that the first two of these play any important part, nor is there any evidence that an intake of food above the requirements at the moment leads instinctively to a subsequent increase in bodily activity. Storage, of course, is a well-established method; the question of luxus consumption requires further consideration.

It is a noteworthy fact that body weight normally tends to remain remarkably constant in spite of wide fluctuations in food intake and bodily activity. The body would appear to have some means of automatically regulating its weight. One of the means by which it adapts itself to under-nutrition is a lowering of the metabolism, so that it would not be surprising if it responded to over-nutrition by an increase in metabolism. Conclusive proof of the existence of luxus consumption in man is not yet forthcoming, but the available evidence points strongly in that direction. As to the bearing of this hypothesis upon the problem of obesity, the first question it raises concerns the definition of over-feeding. From one point of view over-feeding is an excess of food intake over energy requirements. In this sense most people over-eat. But if over-feeding is to be regarded as an intake of food in excess of that which can be dealt with normally by the mechanism regulating the standard of body weight, then fewer people may be said to over-eat. If luxus consumption is involved in the mechanism it follows that its normal limits must be ascertained before a satisfactory definition of over-eating can be given, and this can only be determined after examining a large number of individuals. At present we can only surmise the amount of luxus consumption which might be expected to occur normally. The average intake of food per head of population is approximately 3,400 calories (Atwater), and the average physiological requirement is only 2,500 to 3,000 calories, so that there is an excess of 400 to 900 calories per head, yet only a small proportion of the population is made up of obese persons.

Since luxus consumption, as observed in the dog, varies with the food intake, increasing up to a certain point as the food intake is increased, it would constitute an important protection against obesity. Variations in luxus consumption would explain the differences found in individuals, from those at one end of the scale who remain lean on a very large food intake, and those at the other who tend to put on weight in the presence of even slight excess. From these and other considerations it would appear that the various factors discussed under the heading of energy requirements and energy balance ought to be viewed in their possible relation to luxus consumption. Variations in these factors would be significant in regard to the genesis of obesity only in so far as they resulted in a load being thrown upon luxus consumption beyond the capacity of the mechanism to deal with adequately.

Intermediary Metabolism

A diminution in luxus consumption might be brought about primarily by decreased burning of the excess food or by increased storage. Deficient combustion seems to be a factor only in the small group of obesities associated with a lowered metabolic rate, and especially with diminished thyroid activity. Removal of the gonads is said not to reduce luxus consumption, but no more does it produce obesity in most animals. In the human subject the tendency to obesity after ablation of the gonads increases with advancing years, but this may be due to failure of compensatory changes in the thyroid and pituitary glands. There is no evidence that the obese exhibit any specific inability to burn fat, whether the fat is administered or derived from the fat depots during starvation; nor that the liver, which is supposed to be concerned with converting fat into a form suitable for oxidation, is at fault. There is likewise no evidence of any specific inability to burn carbohydrate.

There remains the second alternative, that the diminution in luxus consumption may be brought about by increased storage. This might be due to some abnormality referable to the fatty tissues themselves, or it might be caused by some disorder of intermediary meta-

bolism leading to increased formation of fat from other foodstuffs. Inability to break down and mobilize stored fat would result in a progressive heaping up of fat in the depots, but this is not observed in obesity. If it could be shown that the essential peculiarity of metabolism in obesity was an excessive conversion of carbohydrate into fat a relatively simple explanation of many of the facts about the disease would be forthcoming. It is difficult, however, to obtain decisive experimental evidence for or against this hypothesis. There is no evidence that the ingestion of carbohydrate causes a more rapid or pronounced rise in the respiratory quotient than in normal persons, and in any event the respiratory quotient only represents a dynamic equilibrium, in which many different kinds of reaction having opposing effects are concerned, so that it cannot be regarded as a reliable guide to what is occurring.

The importance of the interrelationship of carbohydrate and fat metabolism in obesity is further brought out when the role of the endocrine glands and nervous system is considered. Although there are still important gaps in knowledge, the evidence seems to indicate that lesions or functional disturbances of the endocrine glands and nervous system of a kind leading to obesity lead also to the deposition of glycogen in the liver. In this respect the endocrine obesities would come into line with obesities due to overfeeding. The administration of insulin along with adequate supplies of carbohydrate leads to the deposition of glycogen in the liver, and this has also been used as a means of fattening people. Basophil adenomata of the pituitary gland give rise to marked obesity. The more important features of pituitary basophilism, including obesity, though not hypertension, have been reproduced experimentally in the dog by the injection of pituitary extracts rich in gonadotropic hormones (Thompson and Cushing), and one of the most striking results of this administration was the deposition of an enormous amount of glycogen in the liver cells. A very similar syndrome may result from tumours of the adrenal and thymus glands, possibly with similar effects upon glycogen formation. Partial destruction of the anterior lobe of the pituitary gland in young animals may result in obesity (Cushing), and small tumours confined to the sella turcica, without any possibility of their pressing upon the tuber cinereum, give rise to adiposity and an increased sugar tolerance. The obesity resulting from such lesions, unlike that of pituitary basophilism, is probably to be attributed to deficient secretions (of diabetogenic and thyrotropic hormones?)

Little is known regarding the obesity which sometimes follows ablation of the gonads, but it is possible that it may be due to secondary changes occurring in other endocrine glands, especially the thyroid and pituitary. It has recently been shown that removal of the ovaries in the rat increased the glycogen content of the liver (Gullick, Samuels, and Deuel).

Experimental lesions, tumours, and inflammatory disease of the hypothalamus sometimes result in obesity. There are some experimental data suggesting that lesions in this situation may also lead to increased glycogen deposition in the liver (Foster and Benninghoven). A considerable body of evidence has now been accumulated to show that the hypothalamus has physiological and anatomical connexions with the autonomic nervous system. In view of the existence of such mechanisms it would be easy to understand how lesions or functional disorders in the hypothalamus could influence carbohydrate metabolism through the autonomic nervous system. When the disorder was such as to give rise to a predominance of anabolic (parasympathetic) over katabolic (sympathetic) functions, glycogen storage and obesity might result. The

hypothalamus might also influence carbohydrate and fat metabolism through its nerve supply to the pituitary and possibly to other endocrine glands.

The processes of glycogen formation and the conversion of carbohydrate into fat seem to be linked together in some way, but the exact nature of the underlying mechanism responsible for this interconnexion is unknown. Accumulation of glycogen in the liver, however, does not invariably lead to obesity, for if the glycogen is excessively resistant to mobilization, as in von Gierke's disease, the tissues may be starved.

Sugar Tolerance and Obesity

Examination of the sugar tolerance has been employed as a means of investigating the metabolism in obesity. The carbohydrate tolerance in obesity may be normal, increased, or diminished. An increased sugar tolerance might result from increased functional activity of the islet tissue of the pancreas or from diminished secretion of hormones which antagonize insulin, such as thyroxine and certain pituitary hormones; or, again, it might be due to certain lesions of the hypothalamus in situations similar to those which have been shown experimentally by Davis to be capable of suppressing the hyperglycaemia and glycosuria following pancreatectomy. In this connexion the importance of quantitative relationships is to be noted. The administration of excessive quantities of insulin sufficient to produce hypoglycaemia, or the administration of insulin without an adequate supply of carbohydrate, leads to a disappearance of glycogen from the liver and a loss in weight. That may be one reason why hyperinsulinism associated with pancreatic adenomata is not accompanied by obesity. Similarly the emaciation which is found in complete, as contrasted with partial, destructive lesions of the pituitary, as in Simmond's disease (hypophyseal cachexia), may in part be due to chronic hypoglycaemia resulting from lack of the diabetogenic and gonadotropic hormones. In keeping with this is the finding that after complete experimental removal of the anterior lobe of the pituitary the liver glycogen is not increased, and that which remains appears to be very resistant to mobilization (Corkhill, Marks, and White).

Some forms of obesity, on the other hand, are associated with a diminished carbohydrate tolerance often resulting in glycosuria. It is customary to interpret the diminished sugar tolerance as an exhaustion phenomenon due to prolonged overtaxing of the islets of Langerhans and/or to regard the obesity and glycosuria as the result of a common cause—namely, over-eating. This may be the sequence of cause and effect in many instances, but there are many reasons for doubting the validity of this interpretation in all. The most important of these are the results obtained by Thompson and Cushing in their work upon experimental pituitary basophilism, which provide an example of glycogen deposition, obesity, and diminished carbohydrate tolerance produced in a comparatively short time as a result of the administration of pituitary gonadotropic hormones. Evidence is therefore gradually accumulating which points to some forms of glycosuria, particularly those associated with obesity, being due to causes outside the pancreas and possibly referable to functional disturbances of endocrine activity similar to those which occur in pituitary basophilism. But it would not be justifiable to refer all cases of glycosuria associated with obesity to extrapancreatic causes.

The available evidence therefore suggests that the essential change in intermediary metabolism underlying a large group of obesities is to be traced to a disturbance of hepatic function, whereby glycogen is laid down and carbohydrate is converted into fat with excessive ease. This may be

brought about by disturbances in the control of hepatic function due to change in functional activity of one of the endocrine glands, with or without concomitant or compensatory changes in other glands or even in the same gland; or it may be due to changes in the central nervous system. In a very large proportion of cases of obesity, however, there is absence of definite collateral evidence of disease of an endocrine gland or of focal disease of the nervous system. It might therefore be supposed that in such cases the disorder was one of the neuro-endocrine system as a whole, whereby automatic control of constancy of body weight became thrown out of gear. At the same time it is difficult to conceive of a specific anomaly of metabolism affecting all parts of such a complicated mechanism simultaneously, in the absence of some central co-ordinating mechanism. Such a mechanism may perhaps be found in the metabolic centres in the hypothalamic region of the brain or in the neuro-hypophyseal mechanism considered as a functional unit. A functional derangement of this mechanism may be at the root of many cases of obesity—perhaps the majority. Obesity of this variety would be classified as neuro-endocrine.

Distribution of Fat

Can the origin of an obesity be diagnosed from the distribution of fat? An apparently formidable array of evidence has been brought forward supporting this possibility, but I would plead for a more critical attitude. If we confine our attention to the adipose tissue alone, and leave out of consideration all such concomitant phenomena as changes in skeleton, ligaments, skin and its appendages, subcutaneous tissues, genitalia, and so forth, can we be quite certain that the fat is distributed in a characteristic fashion according to the cause of the obesity? If this is not certain, then, in the absence of these concomitant changes, the configuration of the patient would not provide any certain clue to the specific origin of the condition. On the other hand, the physiological variations in the distribution of fat appear to be of so similar a character to those met with in disease that the possibility cannot be overlooked that the fatty tissues themselves, the inherited pattern of the fat depots, may to a large extent determine the distribution of fat in obesity from any cause. Even in obesities of known endocrine origin differences may occur in the distribution of fat in affections of the same gland, while the distribution may be very similar in diseases of different glands. The role of the fatty tissues is also probably of primary importance in another variety of obesity. There are some stout persons who live an active life, eat in moderation, and maintain a fairly constant body weight, but who exhibit no abnormal tendency to put on weight on a liberal diet and in whom no disorder of metabolism is detectable. In these the obesity appears to be structural and developmental rather than metabolic in origin. There seems no reason why the mass and distribution of the fatty tissues should not be determined by heredity, in much the same way as the size and structure of bones or the mass of muscles is so determined, granted, of course, modification by other factors.

The aetiology of obesity may be summed up in the classification of the condition as developmental, metabolic, or nutritional. Metabolic obesity may be endocrine, neurogenic, or neuro-endocrine in origin. The developmental group would be wholly hereditary, the nutritional group wholly acquired, while the metabolic group might be either hereditary or due to acquired disease. In all varieties such variables as food intake and exercise play a part, although in the nutritional group they are the primary factors; while the influence of heredity is suggested by the fact that some 70 per cent. of the subjects of obesity have overweight parents.

TREATMENT OF MAMMARY CANCER*

BY

H. M. MORAN, M.B., CH.M.SYD.,
F.R.C.S.ED., F.R.A.C.S.

DIRECTOR FOR RADIUM THERAPY, THE PRINCE HENRY HOSPITAL,
SYDNEY; CONSULTANT FOR RADIUM, ROYAL PRINCE
ALFRED, LEWISHAM, AND ROYAL NORTH
SHORE HOSPITALS, SYDNEY

The amputation after α -radiation of breasts affected with cancer has enabled us to make observations which, in the main, accord with those of other writers. Unfortunately, since it is not our custom to make a preliminary biopsy, it was not possible to compare conditions before and after irradiation; and, since in growths not subjected to irradiation there is a wide variation in the amount and character of the fibrous tissue and of the small round-celled and plasma-celled infiltration, it was difficult to draw positive conclusions concerning the degree of induced change. There was also no opportunity for correlating the amount and character of the fibrous tissues in the dermis and glandular tissue with the time interval between irradiation and the operative removal of the breast.

Tissue Changes in Breasts Amputated after X-radiation

I am indebted to Dr. A. H. Tebbutt, who has had considerable experience in the histological examination of mammary cancer, for his opinions concerning the changes found in a limited number of breasts amputated after α -radiation. The non-malignant glandular tissue near to, and at some distance from, the growth showed remarkably little effect beyond an increase of the fibrous tissue in and around the lobules. Certainly the gland cells did not show the heteromorphism which was a conspicuous feature of the tumour cells lying at the same depth. Tebbutt did not find the vascular lesions playing the dominant part attributed to them by Pullinger and others. The most striking effect was a morphological change in the irradiated cancer cells and in their subsequent generations, the "formes monstreuses" of French writers. These changes were seen distributed not only throughout both the superficial and the deep parts of the growth, but also in the irradiated metastases in lymph glands. Thus there was not apparent that striking difference between the effects produced on the primary lesion and on the glandular metastases which we see in cervical cancer.

After irradiation the mammary cancer cells often showed a large nucleus, which at times was vacuolated, irregular in shape, lobulated, hyperchromatic, or had an irregular distribution of chromatin. At other times the nucleus was ill defined, pale, and vesicular. The cytoplasm was often abundant, but poorly defined from that of adjacent cells. It was frequently hazy, while both nucleus and cytoplasm stained a deep dirty red colour, as if cell death had taken place. Frank areas of necrosis were not conspicuous, and mitotic figures were rare. Some cells, however, did not show this gross heteromorphism, and it could not be said that the morphological changes described were necessarily indicative of a lethal effect, although the changes produced on cell life and mitosis were profound.

We must accept it as a fact in a discussion of the radiation treatment of mammary cancer that, apart from a few highly anaplastic and relatively infrequent types, the overwhelming majority of these widely differing growths do not possess the distinctive quality of radio-sensitiveness in such a degree as to justify the prior expectation of a cure by these means. It might appear that the breast, by reason of its accessibility, would offer

* Read in opening a discussion in the Section of Radiology at the Annual Meeting of the British Medical Association, Melbourne, 1935.