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ON ADIPOSITY*

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It is common knowledge that fat plays an integral part in the structure of most cells of the body, and in particular those in the central nervous system, but this lecture concerns itself solely with a group of cells which appear to have as their exclusive function the retaining and mobilizing of fat within the cell membrane. These cells produce the lard used in cooking, which the Greeks called *aedepe*—the parent word of adipose tissue. Adiposity thus implies an excess of fat in these cells. The more commonly used word "obesity," meaning excessive adiposity, is a nineteenth-century upstart. It was rarely used before this time, and even at the end of the eighteenth century, though the word was included in Johnson's Dictionary, no reference was given to its prior use. It means literally "to eat away," and Webster's Dictionary describes it as meaning lean that has eaten itself into fat. The increasing substitution of "obesity" for "adiposity" during the nineteenth century probably implies a renewal of a long-dead belief, among lay people at least, that adiposity was a disorder of metabolism and a state of ill-health.

In considering this subject, therefore, I have thought it wise to revert to the word adiposity, implying a consideration of those cells which are primarily concerned with fat metabolism.

The first question which arises is whether the cells have sufficient community of function to enable them to be treated as an organ. Without getting lost in the intricacies of semantic arguments, an organ can be defined as that part of the animal adapted by its structure for a particular function; the cells comprising it should be shown to be capable of reacting as a single unit, though admittedly parts of the organ may be isolated by disease and begin to act independently, as happens with adenomata and carcinomata.

It cannot be denied that the increase in adipose tissue seen at puberty, at the menopause, and as a result of excessive food intake, or that the decrease under conditions of starvation, affect the whole tissue so far as it can be examined. In certain lipodystrophies, however, in recurrent lipomata and Madelung's neck, restricted food intake depletes the unaffected part of the organ, while the diseased part retains its independence.

The idea that adipose tissue of the body behaved as an organ is by no means new, and was first advanced by

Todt in 1870. Ever since this time anatomists, physiologists, and embryologists have returned to this concept. Wells (1940) pointed out that the cells from which adipose tissue is derived are developed from the main mesenchymal tissue and can be distinguished from other connective tissue cells. In their embryological state they have a gland-like structure and assume their adult signet-ring shape only when distended with fat. When emptied of fat they revert to the glandular structure, and indeed islets of glandular tissue found in sections of removed fat may give rise to diagnostic difficulties.

Wells (1940) has reviewed the whole subject, and it is difficult to escape his conclusion that this tissue embryologically, pathologically, and structurally behaves as an organ. It is proposed to treat the tissue as such, with the reservation that certain parts, such as the fat pads behind the eyes, the adrenal pad, and the sucking pad, may serve a different or additional function to that of being solely concerned with fat metabolism; to consider what is known about the structure and function of the adipose organ; and, finally, to pass from this to a consideration of those factors which affect its size.

Structure of the Adipose Organ

It has already been stated that the adipose organ is made up of cells capable of containing a large quantity of fat. The amount of fat in relation to water and protein varies greatly, from place to place in the body, and there are wide variations even when fat is taken from the same site. Fig. 1 shows the analysis of tissue taken from six lean subjects and seven obese subjects from approximately identical spots in the lower abdominal wall at operation. It can be seen that there is considerable variation in the constitution of the tissue from individual to individual. It will be noted that the amounts of water, fat, and protein are expressed as proportions of the weight of tissue removed. In order to imagine what happens when an individual passes from leanness to fatness, the organ must be considered as a whole. Increase in size of the organ—for example, to approximately double—would mean that there had been little increase in the total water content, an increase of almost 100% in the amount of fat, and, strangely enough, double the amount of protein. The latter point is of interest. Since it has been assumed that the cells in the organ do not increase in number in obesity, the protein increase probably represents

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additional protein available for metabolic exchanges taking place within the cells, though it is by no means certain that cells do not proliferate. These individual variations in fat, protein, and water content of adipose tissue, however, may be more apparent than real. If the organ were metabolically active, they might only reflect the previous food intake of the individual. It has been shown that the relationship between fat and nitrogen in adipose tissue taken from animals after a fast as compared with the tissue in the fully-fed state may vary greatly. In normal man the overall composition of the organ has been estimated by Keys and Brožek (1953) and others to be 62% fat, 14% water, and 24% cellular matter (Fig. 2).

The next question which arises is the size of the adipose organ in man. Many methods have been employed to estimate this. Whole-body dissections, and particularly the data from those carried out on reasonably normal subjects by Widdowson *et al.* (1951) and by Forbes *et al.* (quoted by Keys and Brožek, 1953), have formed the basic check for all other procedures, but such measurements are rare. Since fat has a quite different density from the remainder of the body (the

lean-body mass), formulae derived from measurements of whole-body density have been used. Measurements of whole-body density can be made by contrasting the weight of the body in air and in water. The methods are complicated by the fact that they must include measurements of the volume of air in the lungs and an assessment of the volume of air in the gastro-intestinal tract.

Reynolds and Asakawa (1950) have employed an x-ray technique in adults for delineating and measuring subcutaneous fat, since most of the organ lies in the subcutaneous layers of the body (Wilmer, 1940). This technique had previously been used in children. A variation of this technique, using skin callipers to measure fat and skin thickness, has also been extensively employed.

Finally, as adipose tissue contains much less water than the rest of the tissues (the lean-body mass), formulae based upon the determination of the extracellular fluid and total body water in relation to body weight have been derived and used to measure the size of the organ. The whole subject has been admirably reviewed by Keys and Brožek (1953).

In summary, there is surprisingly good correlation between the data obtained by these different methods, and there can be little doubt that a reasonable estimate can be obtained of the size of the adipose organ in man.

FIG. 1.—Analysis of biopsy material taken from lower right abdominal wall in six lean and seven obese subjects at operation.

FIG. 2.—Overall composition of adipose tissue in normal human subject (Keys and Brožek, 1953).

FIG. 3.—Comparison between adipose tissue in female subjects aged 40 with gain in weight of 20% due to adiposity.

TABLE I.—Approximate Relationship Between Body Mass and Adipose Tissue in Man

		Age 25	Age 40	Age 55
Males	Weight	70 kg.	70 kg.	70 kg.
	Adipose tissue	9.9 kg. (14%)	15.4 kg. (22%)	17.5 kg. (25%)
Females	Weight	60 kg.	60 kg.	60 kg.
	Adipose tissue	15.6 kg. (26%)	19.2 kg. (32%)	23 kg. (38%)

Table I has been compiled from the data obtained by these methods and represents the approximate size of the adipose organ in adults of the two sexes at different ages. For the sake of clarity no allowance has been made for the usual increase in weight occurring through the years. Males are regarded as having a weight of 70 kg. and females of 60 kg.

Table I shows that at all ages women have a larger adipose organ than men, and there can be little doubt that this is a true biological variant. The reasons for the increase in size with age are less certain. It may also be a biological variant, but, on the other hand, it has been contended by some that increase in weight with age, and therefore in the size of the organ, is neither biologically necessary nor desirable. At the moment there is insufficient evidence to decide this point, but the increase of size with age must be considered commonplace, at least in the Western world.

If any of these subjects were to become obese there would be no increase in the lean-body mass and no increase in the cell mass in adipose tissue. Thus, a total increase in weight would be represented by fat, except for 10–20% which might be represented by water. A woman of 40 weighing 60 kg. becoming 20% overweight would thus increase to 72 kg., of which the adipose organ would now represent 34 kg. Thus the proportion of body weight represented by fat would rise from 32% to 49% (Fig. 3).

The adipose organ, therefore, is very large indeed—representing about one-fifth to one-quarter of the total

body mass in normal subjects, and capable of increasing to over half the body mass.

Adipose tissue is usually thought to be poorly supplied with blood. This belief is probably based, firstly, on its pale colour as compared with muscle and, secondly, on the observation that it bleeds little at operation. Gersh and Still (1945), using a dye-injection technique and special staining methods, claim that in fact it has an extensive blood supply, which differs, however, in structure from that in other organs. It is composed of a loose network of very small vessels, and the authors have estimated that the capillary density in the adipose organ is at least equal to that of poorly supplied muscle. If, however, the capillary density be recalculated in terms of active metabolic tissue the blood supply is much richer than in most muscles.

Certain further details about the structure of the fat organ may be important. In the subcutaneous tissue the iodine number of the fatty acids decreases and the fat becomes more saturated as the sample taken gets further from the skin. This observation seems to imply that the organ is able to desaturate fatty acids (Henriques and Hansen, 1901; Wertheimer and Shapiro, 1948). Newborn infants have saturated fat at all levels, and this is thought to be concerned with the higher environmental temperature *in utero*. This change in saturation is also associated with a change in the physical properties of fat, and this in turn may be important in altering the rate of heat loss from the organism as a whole.

Functions of the Adipose Organ

There can be little doubt that the main function of the adipose organ is concerned with energy exchanges in the body. It shrinks when food supplies diminish and increases when there is excessive food intake. Furthermore, Newburgh (1942) pointed out that the diminution in size of the organ bore a relationship to the deficiency in calorie intake of the individual. Fig. 4 confirms the observation (Kekwick and Pawan, 1956).

Until recently the usual idea of the function of the adipose organ was that it was a static energy store,

FIG. 4.—Daily changes in weight in six patients, each on diets of identical composition but different calorie value. (Mean figures of seven- to nine-day periods on each diet.)

taking up surplus energy under conditions of excess eating, storing it in the form of fat, and giving it up when food intake was too little. Excessive size of the organ resulted from excessive calorie intake.

The implication of this idea is that the fat depots take little part in the day-to-day and minute-to-minute metabolic changes going on in all tissues. If this were so, it is difficult to see why the adipose organ should have the large blood supply alluded to above, unless it be assumed that this was for use only in times of emergency.

Animal Studies

The classical concept of adipose tissue as an inert depot needs further examination to-day in the light of modern information obtained from *in vitro* studies of surviving strips of such tissue and recent extensive experimental work on animals. The *in vitro* studies of Shapiro and Wertheimer (1956) on surviving adipose tissue have shown that its oxygen uptake is high. It is also dependent on the previous nutritional state. Fatty tissue removed from a fasting animal has an oxygen uptake of 0.12 c.mm./hr./mg. After a period of fasting followed by a carbohydrate meal, the figure rises to 0.18 c.mm./hr./mg. (Mirski, 1942). That is to say that slices of adipose tissue have a metabolic activity about equal to that of kidney tissue and about half that of liver.

Extensive studies on intact animals, using deuterium or radioactive carbon as labels, indicate that half the adipose organ in normal rats and mice is metabolized and reconstituted in the incredibly short period of five to nine days (Bernhard and Schoenheimer, 1940; Stetten and Grail, 1943; Buchanan and Hastings, 1946). Certain hypothalamic lesions produce gross obesity to a point where the mice become about four times their normal weight (Mayer, 1957). The animals become voracious and even have to be prevented from choking themselves to death with food. The rate of turnover in the fat remains normal and the enlargement of the adipose organ depends on excessive deposition of fat. In certain congenitally obese animals, on the other hand, the same weight can be attained though the increase in appetite is less apparent. The obesity is produced in part by diminution in the rate of turnover, which slows down from a rate of five to nine days to a figure of about 90 days (Salcedo and Stetten, 1943). That alteration in the rate of turnover may affect the size of the organ is confirmed by the marked differences found in the amount of carcass fat as between the congenitally obese mice and the hypothalamic obese animals—when both are subjected to food deprivation sufficient to reduce them to the same weight (Hollifield and Parson, 1958); the carcass fat remaining much higher in the congenitally obese animals even though the total body weights are the same.

Such observations give a very different picture of the function of the adipose organ in animals. Far from being a comparatively static energy store for use in times of emergency, the organ appears to have a high metabolic activity, with a high oxygen uptake and a rapid rate of turnover. If these observations are accepted, the adipose organ must be taking part in the day-to-day energy exchanges of the organism as a whole.

Transposition of these figures direct to man give an astonishing picture. A normal woman of about 60 kg. weight at the age of 40, who had a fat-turnover of this

order, would be forming and destroying at least 1.5 kg. of fat every 24 hours. The intake of such a subject over the same period would probably comprise only some 60 g. of fat and about 400 g. of carbohydrate. If all the fat and half the carbohydrate in the diet were deposited as fat and exchanged in the adipose organ, this would account only for 150 g. a day—that is, 10% of the amount exchanged. The remaining 90% must presumably be synthesized from substrate brought to the organ by the blood-stream which is then being returned to the blood-stream in one form or another. This conclusion seems so unlikely that it must cast doubt on the techniques of estimating turnover rates. It has already been suggested by us that the most recently deposited fat may be most readily mobilized (Chalmers, Kekwick, Pawan, and Smith, 1958). If this were true a falsely high rate of turnover would be obtained from the interpretation of results using C14-labelled fatty acids recently administered.

It is fully realized that conclusions based on animal experiments do not always hold for man, and one must ask the question whether evidence exists to support the contention that such activity does indeed take place in man.

Studies in Man

No direct measurements of turnover using labelled fat have been made in the human subject, but there is abundant evidence in relation to the oxygen consumption of the adipose organ. It has already been pointed out that the obese only differ from the lean by the greater size of their adipose organ, and it is almost universally accepted that they have normal B.M.R.s. The B.M.R. is calculated from the oxygen uptake, an assumed figure for the respiratory quotient and expressed as a function of body weight and height (body surface). If fat were metabolically inactive the oxygen uptake of an obese subject should be comparable to that of a lean subject. If this were so, the B.M.R. in the obese therefore could be measured by taking the oxygen uptake, using the assumed respiratory quotient, and expressing this figure as a function of a lean subject of the same height but of normal weight. The carrying out of this procedure gives figures for B.M.R.s in the obese of the order of +20% to +50% (Strang, 1959). However, neither the cardiovascular, the respiratory, nor the central nervous system shows evidence of such unusual activity. The usual explanation, that the obese are under the strain of having to move their increased weight, does not hold under basal conditions. Indeed, under these conditions the obese are accepted as being less active, breathing more shallowly and less rapidly than normals, and having normal heart rates. The obvious explanation that the fat itself uses the extra oxygen appears to have been neglected.

If it is accepted that it does so, then adipose tissue in man has approximately the same oxygen uptake as the lean-body mass and its contained fluids—that is, about 0.2 c.mm./hr./mg., a figure comparable to the direct measurements of Shapiro and Wertheimer (1943) on isolated fat tissue of animals.

A further piece of indirect evidence also exists. The rate of turnover in the plasma of non-esterified fatty acids (free fatty acids) labelled with radioactive carbon has been measured in man. These substances, which probably represent the main form in which fat is conveyed from place to place in the body, are turned over in the blood-stream at an extremely rapid rate. Half

the injected material is cleared from the blood-stream in one to three minutes, and one-quarter of the total plasma pool is therefore turned over every minute (Fredrickson and Gordon, 1958). This is many times faster than glucose; the comparable figures for the percentage turnover of the plasma pool a minute being approximately 0.7% for glucose and 28% for free fatty acids (Dole, 1960).

In summary, there appears to be direct evidence in animals and indirect evidence in man that the adipose organ is a highly active metabolic tissue with a turnover rate far more rapid than can be accounted for in terms of fat and carbohydrate intake.

Conflicting Hypotheses

It has been accepted that the main function of the adipose organ is almost certainly concerned with the energy needs of the body, since it shrinks under conditions of low energy intake and increases under conditions of high intake. It is from this point onwards that two conflicting points of view arise. The first is that the adipose organ is a relatively inactive calorie store, and the second is that the adipose organ is in a state of constant metabolic activity, taking part in the hour-to-hour and minute-to-minute metabolic changes of the body.

It is possible to examine indirectly which of these hypotheses is correct in two further ways. Firstly, where the total energy output of the body is known to be low, as in myxoedema, or after removal of the thyroid gland, the adipose organ should be normal in size under the first hypothesis if appetite is reduced commensurately with reduced energy output or greater than normal if appetite reduction has been insufficient. It would be unlikely to be less than normal. Under the second hypothesis, the adipose organ, however, might be expected to be reduced in size, as its function in relation to energy supply would be required to a less extent. Secondly, if exactly the same calorie intake in animals or man is maintained for a reasonable period of time, the resultant size of the adipose organ at the end should be identical in all under the first hypothesis but could only be different under the second.

Direct experimental evidence concerning the adipose organ after thyroidectomy was obtained by Mackay and Sherrill (1941). Three sets of adult rats were fed for 310 days on high-calorie and high-fat diets. The first acted as a control, the second were thyroidectomized, and the third were given thyroid extract. At the end of 310 days the weights of the control and thyroidectomized animals were the same, but carcass analyses showed that fat comprised 31.1% of the body weight in the controls and only 6.4% in the thyroidectomized animals. The results are illustrated in Fig. 5. (This may not hold when thyroidectomy is performed at a time when the animals are growing (Scow, 1951)—

FIG. 5.—Body composition of three groups of rats after period of 310 days. Data of Mackay and Sherrill (1941).

an experimental result which accords with the observation that cretins tend to have an increase in body fat.)

There is also evidence in relation to this point in man. Plummer (1940) reviewed the nutritional state of 200 patients with primary myxoedema. He found that 38.5% of them were under standard weight for height and only 61.5% were either normal or above normal weight. It is recognized that some of the weight of these patients is represented by the deposition of myxoedematous tissue. As soon as these patients are given thyroid extract they go into negative nitrogen balance and rapidly shed the abnormal tissue. This rapid shedding of weight for the overweight group was measured. It represented an average of 5.9 kg. per person for the group as a whole, whereas the subjects on the average were only 4.6 kg. overweight. In short, Plummer concluded that hypothyroid patients were in fact grossly underweight when allowance is made for the myxoedematous tissue. It would appear, therefore, that, both in animals and in man, lowering of the metabolic activity of the organism as a whole is associated with a shrinking of the adipose organ. It is possible to argue that too much has been made of this shrinking in hypothyroid states, since the converse is manifestly untrue. None the less, the conclusion that the adipose organ decreases in states of low metabolic activity is probably important.

Evidence respecting alteration in size of the adipose organ when diets of equal calorie intake are given is

FIG. 6.—Changes in body composition of rats eating *ad lib.*, isocaloric force-fed rats, and underfed animals. Data of Cohn and Joseph (1959).

also available. The paired feeding experiments of Cohn and Joseph (1959) are impressive. One set of rats were allowed to eat *ad lib.* The amount was measured and a second set of animals were fed twice a day, by stomach tube, with exactly the same type and amount of food as the first. A third set were force-fed on 20% less food and acted as controls. At the end of the experiment the animals were sacrificed and analyses of the carcasses undertaken. The first and second sets of animals weighed the same at sacrifice, but the animals fed *ad lib.* had increased their body fat by 4.5%, though the force-fed animals having the same calorie intake had increased their body fat by 13.2%. The controls had less body fat and had gained less weight, as might have been anticipated. The results are illustrated in Fig. 6.

TABLE II.—Comparison of the Effects of Repeated Injections of Saline, Non-fasting Urine Extracts (NF), and Fasting Urinary Extracts (F). Each Animal Was Given 0.5 ml. on Alternate Days for a 17-Day Period

	No. of Animals	Mean Food Intake (% of Control)	Body Weight Change in g./Mouse/Day	Carcass Analysis (% Body Weight)		
				Fat	Water	Protein
Saline ..	30	100	—0.109	13.5	64.3	11.9
NF ..	10	101	—0.118	13.4	63.7	11.8
F ..	20	98	—0.360	11.8	66.1	13.6

In reverse, Chalmers *et al.* (1958) have shown that after the injection of a urinary extract from fasting human subjects mice lose weight over a period of three weeks as compared with controls having either saline injections or urinary extracts from subjects who are feeding normally, even where the food intake of the

FIG. 7.—Daily loss of weight of patients on 1,000-calorie diets of different composition. (Mean figures of five- to nine-day periods on each diet.)

two sets is equal. Carcass analyses show this loss of weight to be about 70% fat and about 20–30% water (Table II).

In man, isocaloric diets fed to obese subjects in rotation produce different rates of weight loss over short periods (Fig. 7). Measurements were made of their food absorption, nitrogen balances, and total body water. It was concluded that some 70% of the weight lost in all groups is represented by loss of fat (Kekwick and Pawan, 1956, 1957). It would therefore appear as though the resultant size of the adipose organ in man may be changed after short periods on different diets of equal calorie value.

It was submitted theoretically that such findings could be made only if the adipose organ was in a constant state of activity, and it seems reasonable to conclude that this is indeed the case both in animals and in man.

If fat utilizes oxygen, then the organ almost certainly conforms to the present concepts of tissue behaviour (Brody, 1955)—namely, that oxygen is required for the synthesis of high-energy substances or bonds and that the breakdown of these with consequent energy release requires no oxygen. In most tissues some 70% of energy is released in the form of heat and the remaining 30% for the essential needs of the organ. It is now possible to speculate on what these special needs may be in the adipose organ. Energy would be required for synthesis of fatty acids—for releasing fatty acids for use by other organs (*Lancet*, 1959)—and possibly desaturating fatty acids within the adipose organ to maintain body temperature.

If substances exist in the organ which affect the percentage yield of essential energy as compared with heat energy, alterations in its size could be achieved without any alteration in oxygen uptake (Portman and Hegsted, 1957).

One can now review the problem of adiposity in the light of these conclusions. The simple statement that obesity arises when calorie intake exceeds output is of course unchallengeable. Under the present hypothesis, however, it represents the truth but not the whole truth, and the problems of increase or decrease in size of the adipose organ resolves itself into a study of the factors governing the laying down of fat in the adipose organ and the control of its mobilization.

Fat Deposition

Not a great deal is so far known about the control of fat deposition. There can be little doubt that almost all the fat taken into the body as food is deposited in the fat organ, even when administered in amounts below the calorie requirements of the organism (Rittenberg and Schoenheimer, 1935). In phloridzin-treated animals there is a sharp increase in blood lipid levels coincidental with a diminution of the size of the adipose organ, so that fat deposition does not appear to be a passive transference to the cells from the blood-stream. Furthermore, in isolated surviving fat tissue, fat deposition is shown to be halted by temperatures over 80° C. and by the addition of sodium fluoride or sodium cyanide, so that deposition appears to be an active metabolic process (Wertheimer and Shapiro, 1948).

There is little doubt, also, from *in vitro* studies of adipose tissue, that glycogen appears intracellularly in fat tissue if the animal has fasted for a period and then eaten carbohydrate. It precedes fat deposition and disappears coincidentally with the cessation of fat formation (Tuerkischer and Wertheimer, 1942). These studies also show that the tissue has a respiratory quotient above 1, a finding that almost exclusively indicates the conversion of carbohydrate to fat. There seems little doubt, therefore, that carbohydrate can be, and probably is, a major precursor of fat. Single doses of insulin to animals fed normally leads to the appearance of glycogen in adipose tissue and the acceleration of fat deposition (Wertheimer, 1945).

In similar *in vitro* studies fasting has been shown to inhibit lipogenesis (Hausberger and Milstein, 1955). In

view also of the work on obese patients already quoted (Kekwick and Pawan, 1956, 1957), it is interesting that Hausberger and Milstein found that the previous intake of a high-fat diet inhibited lipogenesis in isolated tissue removed from the animal.

In the intact animal there is ample evidence that a supply of food is necessary for fat deposition. It would appear that deposition largely ceases under conditions of starvation and increases where food intake is increased. This is not to say that appetite and satiety alone control fat deposition. The work of Cohn and Joseph (1959), already quoted, indicates that the manner in which the raw materials are supplied is certainly one other factor. Furthermore, studies on animals with hypothalamic lesions who get fat because of their voracious appetites show that the amount of fat laid down is much greater than that in control animals which have been force-fed the same amount of food (van Putten *et al.*, 1955). There must be many other factors related to fat deposition that are unknown, and it is clear that much more investigation will be needed before any coherent idea of this complicated process is achieved.

Fat Mobilization

Many gaps also exist in knowledge about the physiological control of fat mobilization. Studies with high-fat, high-protein, and high-carbohydrate diets suggest (Kekwick and Pawan, 1956, 1957) that the type of food influences the rate of fat mobilization, but the details of this are far from clear (Fig. 7). Hormones which are known to increase the amount of free fatty acid released from adipose tissue *in vitro* are adrenaline, nor-adrenaline, corticotrophin, growth hormone, and a urinary extract from fasting human subjects described previously by Chalmers *et al.* (1958).

We have been particularly interested in this urinary extract, partly because it appears to be important physiologically and partly because, by analogy with the way the body handles water, the control of the output side of the equation appears to be more important in relation to the total volume retained than control of the input factor. The conditions under which it appears in the urine are shown in Table III. Fasting, low-calorie intake, and carbohydrate deprivation give good yields of the substance. Two patients with diffuse lipoatrophy (one associated with diabetes mellitus and increased growth) have shown activity even when taking a normal diet. In six patients with deficient pituitary function, fasting has failed to give any yield at all, which would suggest that the pituitary plays an essential part in the chain of its production.

TABLE III.—Conditions Which Govern Appearance of Fat-mobilizing Substance in Human Urine

Present	Absent
Fasting	Normal diet
1,000 cal. (90% fat)	1,000 cal. (90% CHO)
2,000 .. (80% ..)	Hypopituitarism (fasting)
1,000 .. (90% protein)	
Diffuse lipoatrophy (non-fasting)	
Diabetic ketosis*	
Carcinomatosis*	
Post-operative*	

* Were also on low-calorie and low-carbohydrate diets.

TABLE IV.—Effects of Urinary F.M.S. in Mice

Increases	Decreases
Liver fat	Body weight
Blood lipids	Carcass fat
.. ketones	Blood sugar
Fat utilization	

The biological properties of the substance are listed in Table IV. Injected into mice, it produces loss of weight, the loss being mainly in terms of the carcass fat and bearing some relation to the dose administered (Fig. 8). The food intake of the injected animals is the same as that for the controls injected with saline. It

also produces rises in blood lipids, blood ketones, and liver fat within six hours of injection (Fig. 9), and is capable of liberating free fatty acids from an isolated fat pad (Chalmers *et al.*, 1960a). In structure it resembles, but is not identical with, corticotrophin (Chalmers *et al.*, 1960b), it is adsorbed on to oxycellulose, and has a weak melanophore-stimulating action. However, it is not identical with corticotrophin, since it exhibits none of the usual steroid-like effects in the intact animal, has only very low activity in releasing steroids from viable adrenal tissue, and after inactivation by hydrogen peroxide cannot be reactivated with cysteine. Nor does corticotrophin produce loss of fat in the intact animal.

Fat mobilization itself probably mainly represents a release of free fatty acids from the adipose organ in view of the very rapid turnover of free fatty acid in the plasma pool (28% of the pool every minute), but these in turn can and do provide the major metabolic fuel for most tissues. Evidence has recently been put forward to suggest that fat may also be turned into carbohydrate, with a net gain of the latter substance (Kekwick *et al.*, 1959), and it is possible that part of the mobilization may take the form of converting fat into carbohydrate.

As with fat deposition, much more requires to be known of all these factors and the homoeostatic mechanisms which balance them before control can be exercised over the size of the adipose organ.

Conclusion

It cannot be pretended that these ideas of the structure and function of the adipose organ will stand the test of all further investigations and remain unchanged, since many of them are, of necessity, based upon imperfect evidence. It is only suggested that perhaps they are more nearly related to the true state of affairs than previously held views that fat exists as an inert calorie store. If so, the subject of adiposity becomes open to assault by different means than those previously employed.

The subject of adiposity is one of importance. It has been described as one of the major health hazards in modern life in the western world. Whether this be true or not, there is little doubt that people with enlarged adipose organs are unhealthy; that they die prematurely; that they are prone to diseases such as hypertension, diabetes, cholecystitis, and osteoarthritis; and that many of them are psychological cripples.

Public intolerance of this condition has never been so intense, as evidenced by the interest taken in the subject in almost every newspaper and magazine. This is in contrast to the somewhat resigned view taken by the medical profession of which Banting (1864) was complaining 100 years ago. Doctors too often tend to blame their long-term failure to relieve obesity on the gluttony of their patients. It is submitted that satisfaction with the too simple view that fat represents an inert calorie store has retarded and is retarding developments in this field.

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FIG. 8.—Loss of weight in mice after a single dose of F.M.S. in different doses. Food intake (g.): Control 7.0; 0.4 mg., 8.1; 4 mg., 7.9; 40 mg., 8.0.

FIG. 9.—Effect of F.M.S. on blood sugar, blood ketones, and liver fat after injection into mice.

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"There is prevalent amongst all Africans the injection craving." This perhaps originated from the fact that at the turn of the century there were outbreaks of diseases that could be cured or prevented by making scarification marks or by giving prophylaxis by injection and also curative measures by injections, e.g., yaws and N.A.B. or bismuth. This form of curative approach came near to the African's way of effecting cure for all sorts of diseases, which was by making scarification marks and breaking the surface of the skin and rubbing in medicine. The belief was that by so doing the medicine entered the blood and through this reached all the system. Thus an injection inserted into the buttock or into a vein carries a notion as near to the old belief as possible." (Dr. W. Ouko: 3rd Conference of East African Branch of the Society of Medical Officers of Health, *E. Afr. med. J.*, March, 1960.)

WHY THIOPENTONE INJECTED INTO AN ARTERY MAY CAUSE GANGRENE*

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In 1948 the Swedish worker Schmitterlöw showed that if he made an extract of arteries or of veins from a horse or an ox the extract contained noradrenaline. His observations, however, did not lead him to suggest that the presence of noradrenaline in the artery wall had any importance, and no further attention was paid to it until 1957, when Burn and Rand showed that the day after rabbits were injected with reserpine the aorta no longer contained appreciable amounts of noradrenaline. Whereas the thoracic aorta from normal rabbits contained a mean quantity of 0.52 $\mu\text{g./g.}$, the aorta from rabbits treated with reserpine contained less than 0.08 $\mu\text{g./g.}$ It was also shown that while a spiral strip of aorta from a normal rabbit placed in an isolated organ bath contracted on addition of nicotine to the bath, a similar strip from a rabbit treated with reserpine did not contract. Burn and Rand (1958a) suggested that the constrictor action of nicotine was due to the release of noradrenaline from the store in the artery wall.

Another substance which was found to be inactive in the animal treated with reserpine was tyramine. Carlsson, Rosengren, Bertler, and Nilsson (1957) showed that while tyramine caused a rise of blood-pressure in an anaesthetized cat it failed to cause a rise of blood-pressure in a similar cat previously treated with reserpine. This observation was confirmed (Burn and Rand, 1958b), and several other amines related to tyramine, among them amphetamine and ephedrine, were shown to behave in the same way. While they were able to raise the blood-pressure in a normal animal, they were unable to do so in an animal which had been previously treated with reserpine.

These observations showed that substances which cause constriction may do so in two ways. They may constrict the blood-vessels themselves like adrenaline and noradrenaline, or they may act indirectly by liberating noradrenaline from the store in the artery wall.

Action of Thiopentone

There has been a series of recorded accidents in which an anaesthetist has injected thiopentone into an artery by mistake, probably because of the aberrant course of the artery. The incidence has been variously estimated from 1 in 8,000 (Lundy, 1942) to 1 in 55,000 (Cohen, 1948). Out of 24 cases, nine developed gangrene, and, of these, six required amputation of the forearm and three lost one or more digits. Professor Sir Robert Macintosh pointed these accidents out to me and asked whether the action of thiopentone could be investigated. It seemed possible that thiopentone might prove to be a substance which released noradrenaline from the store in the artery wall, and experiments were carried out to see if this was so. Observations were first made on spiral strips of rabbit aorta. When 2 mg. of thiopentone was added to a 5-ml. bath the strips of aorta contracted; they relaxed again when the solution in the bath was changed. Observations were then made by perfusing

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