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DISCUSSION ON EXPERIMENTAL APPROACHES TO OBESITY

Dr. G. C. Kennedy: *Experimental Hypothalamic Obesity.*

Physicians have recognized for a long time that obesity is associated in some way with the hypothalamic-pituitary complex. Fröhlich (1901) traced descriptions of gross obesity with tumours of this region in the clinical literature as early as 1840. Both he and Babinski (1900) related the obesity to diminished secretion of the pituitary. But Erdheim, in 1904, held that it was due to damage to the hypothalamus, and subsequent clinical work has done little to settle the controversy. Unfortunately, pathological processes are seldom so localized that they can be said with confidence to be entirely glandular or entirely nervous. However, in the last ten years experimental studies of hypothalamic obesity in animals have done something to simplify the position.

Ever since 1913, when Camus and Roussy showed that hypophysectomy in the dog never caused an increase in weight unless the base of the brain was damaged at the same time, there have been attempts to produce pure hypothalamic obesity experimentally. But it was not until 1939 that S. W. Ranson (Hetherington and Ranson, 1939) was able to do it regularly by making small electrolytic lesions in the brain with an electrode introduced from above, leaving the pituitary intact. Brobeck, *et al.* (1943) improved the technique, used much smaller lesions, got much more striking obesity, and showed that bilateral damage to the nuclei of the tuber cinereum was the essential lesion. In 1943, Hetherington, one of Ranson's colleagues, showed that hypophysectomy either before or after the hypothalamic operation failed to prevent the obesity, and concluded that the pituitary played no part in its production. The original work was done on the rat, but it has been confirmed in the cat, the dog and the monkey.

Although, clinically, cases of obesity where one can demonstrate organic damage to the hypothalamus are rare, I think one can learn something from the behaviour of these rats which may help towards an understanding of obesity in general. I shall restrict this description to some of the points which suggest analogies with human obesity. The animals I shall describe have been prepared by Brobeck's technique.

The obesity causes an enormous increase in weight, and a gross change in appearance compared with an unoperated control rat, but there is no effect on skeletal length, although most of the operations were carried out during a period of active growth. This in itself is strong evidence of the absence of any pituitary damage. The fat is distributed fairly uniformly through all the usual depots. By comparison the parenchymatous organs are spared—for example, in rats which have yielded over 50% of fat from the body as a whole the liver fat has been less than 10%.

The rat's hypothalamus is extremely small—only about 3 mm. across—and more than one hypothalamic centre may be involved in an experimental lesion. So obesity may be associated with diabetes insipidus, genital atrophy, somnolence, aggressive behaviour and so on after the fashion of the syndromes of clinical medicine. But these are not regular associations, and it is possible to produce fat rats in which the only detectable abnormality is the adiposity.

The immediate cause of the obesity, without any doubt, is overeating. Investigations of metabolic rate, intestinal absorption, spontaneous activity and so on have been carried out in various laboratories to see if these rats utilize their food better than normal ones, or save energy in any way, but they have all been negative. However, as soon as the animals recover from the anæsthetic after operation, it is obvious that their feeding behaviour is abnormal. They will attack and eat anything within reach while they are still confused from the anæsthetic; once fully recovered they are not so omnivorous, but under optimal conditions they will eat twice to three times as much as an unoperated rat in the first day, and may keep up this high intake for four to six weeks.

As the obesity develops, the food intake decreases, and we have found repeatedly that once the obesity is established a rat can maintain a weight of about 50% above normal indefinitely without any significant increase of food intake. As the animal gets fatter and its surface area increases, its basal metabolic rate must increase, but this appears to be balanced by some decrease in activity. However, we have never had a fat animal that ate less than its control. And at any stage if one gets the weight down by putting the animal on short rations for a time, then restores unrestricted feeding, the original high food intake returns and the rat gets fat again. I shall refer to this high food intake by Brobeck's term of hyperphagia.

Detailed analyses of operated rats have been published (Kennedy, 1950). They show that the increased weight is all accounted for as fat, and there is no change in the amount of body water, or in the dry, fat free fraction of the carcase. Our heaviest rats have weighed over 700 grammes, which is more than twice the weight attained by their controls, and some have contained as much as 65% of fat. Eventually the enormous accumulations of fat appear to be lethal. We have used young rats for operation which would normally have a further expectation of life of at least two years. They seldom survive for more than a year.

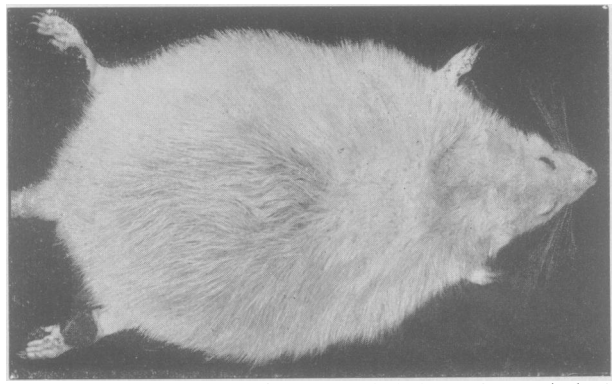

FIG. 1.—Obese rat twenty-eight weeks after operation. Trophic lesions of the skin had already developed, but the kidneys were histologically normal.

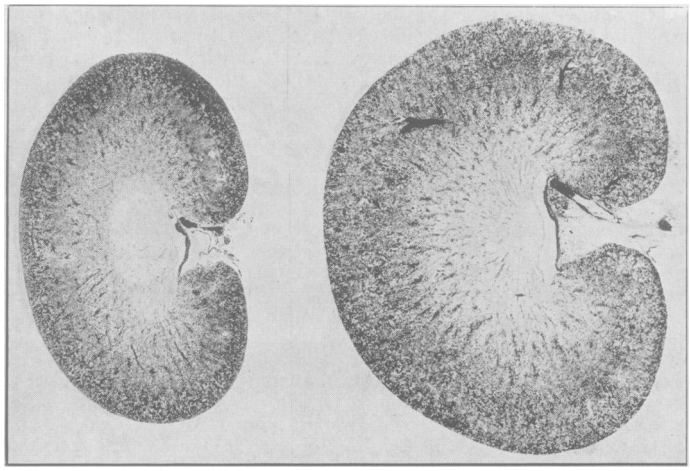

FIG. 2.—Kidney enlargement in obese rat (right) compared with kidney of litter mate control (left) sixty-three weeks after operation. Weight of obese rat 620 grammes, control 250 grammes. × 3.

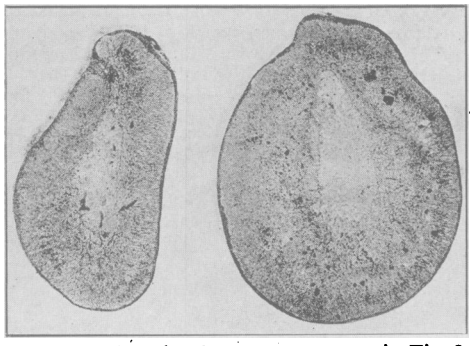

FIG. 3.—Adrenals of same two rats as in Fig. 2. × 7·5.

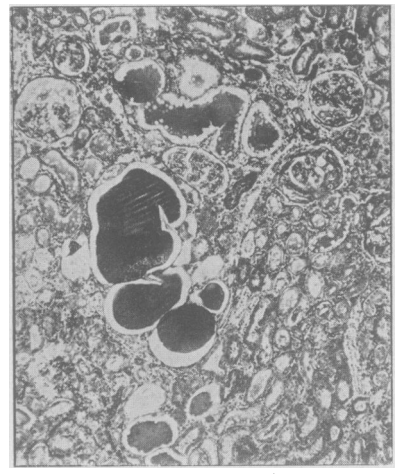

FIG. 4.—Higher power view (× 57·5) of abnormal kidney from Fig. 2. This shows a late stage of the lesion, in which the glomeruli as well as the tubules had become involved.

After six to eight months they develop trophic lesions of the skin. Fig. 1 shows a rat at this stage with large pressure sores on its feet, and a good deal of loss of hair from its back. Such animals show considerable delay in healing of wounds, even if these are placed in areas such as the back without much underlying fat, and subject to little pressure or friction.

A little later they show gross kidney damage which appears to be a major factor in limiting their survival (Fig. 2). There is severe albuminuria with rapid weight loss preceding death. The enlargement of the kidney is sometimes enormous, and is not matched by any corresponding enlargement of other organs with the exception of the adrenals (Fig. 3).

The damage to the kidney appears to fall primarily on the tubules (Fig. 4). The epithelium becomes atrophic and the lumen is full of hyaline debris. There is relatively little glomerular or vascular damage until a late stage, and although the animals are sometimes hypertensive, this is not constant. We are at present trying to elucidate the mechanism of the kidney damage. Histologically it has the appearance of pyelonephritis, which Goldblatt has shown to be common in some strains of rats. But none of our controls have shown kidney lesions, and we have found no sign of infection at any stage in the fat animals. Although it might be tempting to regard it as due to a relative deficiency of lipotrophic substances, the slight degree of liver involvement is against this. Selye (1950) has shown that histologically similar appearances can be produced in the kidney by a variety of non-specific stresses, and regards the kidney damage as secondary to over-activity of the adrenal cortex. The adrenals are certainly very much enlarged in these animals, and it is possible that obesity represents a stress in the sense in which Selye uses the term.

The feeding reactions of these animals are of some interest. The normal rat appears to be quite indifferent to changes in the palatability of its food. Mixing its stock diet with equal parts of dry kaolin powder, for example, simply results in the animal doubling the bulk it eats, so that its calorie intake is unaffected. In the early stages after operation, a fat rat will eat such a diet in even greater amount than a normal rat does, and will continue to get fat on it. But when the obesity is fully established, the rat is very much more discriminating, and will refuse to eat a kaolin mixture at all until it has used up most of its stored fat. Yet if at this stage the kaolin mixture is replaced by its normal diet, the rat will appear to be much more hungry than its control, eating twice as much as its control does. This effect does not depend in any way on the bulk imparted to the diet by the kaolin. A similar effect on food intake is produced by mild dehydration. Restriction of the water intake of a normal rat to 10 ml. a day hardly affects its food intake. Nor does it affect a hyperphagic rat soon after operation. But it causes considerable depression of food intake in fully developed obesity. This is probably only another way of reducing the palatability of food, by drying the mouth slightly. In circles where obesity still seems to be confused with œdema dehydration is often used as a treatment for the obese patient. Its success is alleged to be due to the mobilization of water. As it mobilizes fat just as well, one wonders if the treatment may be the right thing done for the wrong reason.

Pretty well any method of reducing the palatability of food, such as adding unpleasant tasting substances like quinine (Miller, Bailey and Stevenson, 1950) will affect the intake of the fat rat more than that of the normal animal. Conversely, anything which makes the diet more palatable makes the fat rat still fatter, but is without effect on its control. Sometimes merely making the diet into a wet mash instead of feeding it dry is enough to cause a considerable increase in weight.

Satiation in the rat appears to be determined then by two major factors. The intact animal always stops eating when it has got enough calories for its current needs, so it lays down no surplus fat. It is this calorimetric control which is paralysed by operation on the hypothalamus. Then another aspect of satiation becomes more important, represented in our experiments by the various conditioned reflexes affecting the weight of the obese animal. There is no fundamental difference in mechanism—the hypothalamic factor appears to be dominant in the young intact animal, the cortical one in the obese. Older unoperated rats tend to run to fat, and then they show the same reaction to changes in palatability of their diet as the operated animals do.

The basic urge to eat is never permanently reduced by hypothalamic lesions—that is one cannot produce chronic anorexia, although of course any intracranial operation may cause refusal of food for a few days. So hunger itself has probably nothing to do with the hypothalamus. The principal factors controlling food intake according to this hypothesis may be illustrated in a simple diagram.

This represents food intake as being controlled by a balance between hunger and satiety. Satiation has the two major aspects I have described. The release of hunger from hypothalamic inhibition causes hyperphagia. As fat accumulates in the depots a threshold is eventually reached where hunger is again inhibited and hyperphagia stops. As this stage is approached, the cortical aspect of satiation becomes relatively more important.

The nature of the stimulus to which the hypothalamus reacts is a matter of controversy. Brobeck believes it is the heat produced by the ingestion of food. We believe it to be the level of circulating metabolites, whether these are derived from ingested food or from turnover of the fat depots. We have published some of the evidence for this view and are preparing further evidence for publication (Kennedy, 1950; Bruce and Kennedy, 1951).

Obesity is not always due to damage to a hypothalamic centre—quite the contrary. It is common experience that people can be divided into two types so far as their weight control is concerned. The first type can apparently commit any dietary indiscretion with impunity and remain like Cassius, lean and hungry looking. No one can dispose of any appreciable quantity of food after it is absorbed without either burning it or storing it as fat. The restless energy of the Cassius type may account for the burning of considerable amounts of food, but his major bouts of overeating must be balanced by periods of reduced intake. I think it is highly

probable that this is brought about, as in the young rat, by the hypothalamus. But the second, less fortunate type of person maintains a steady weight only by conscious attention to his diet, or by early social training which makes such attention a habit. I think this is the type of person who becomes obese. Like the older rat, he has an inefficient hypothalamus, if indeed he has any hypothalamic control at all. Professor McCance and Miss Widdowson (McCance and Widdowson, 1951) have shown that really obese patients are as fat as the fattest rats which can be produced by hypothalamic operation. As such obesity notoriously follows relatively minor causes—emotional upsets and the like—I find it difficult to believe it can be due to paralysis of a major vegetative centre in the hypothalamus. Obesity in such a person has probably a purely cerebral cause and it would be more logical to call it cortical than hypothalamic obesity.

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Captain Albert R. Behnke, M.C., U.S.N.: *Measurement of the Fat and Water Content of the Body in Relation to Obesity.*

The shortening of life expectancy and the many medical ailments that are associated with obesity constitute a long recognized, serious medical problem. The key to an understanding of the problem of obesity would appear to be a quantitative approach centering in the measurement of the fat content of the body. During the past twelve years there have been developed two reliable methods for *in vivo* fat estimation, one based on the determination of the specific gravity of the body as a whole, the other based on the determination of total body water.

The specific gravity of the body as an index of obesity.—Data obtained by naval investigators since 1939 (Behnke, Feen and Welham [1]; Welham and Behnke [2]; Pace and Rathbun [3]) established the close correlation between the specific gravity of the body as a whole and its fat content.

For the determination of specific gravity the essential measurement is that of body volume which, based on Archimedes' principle, can be determined conveniently by the method of hydrostatic weighing, i.e. equivalent volume = weight in air minus weight in water. The weight in water is determined by suspending a subject below the surface of the water on a line leading up to a spring scale graduated in ounces. A weighted lead belt maintains negative buoyancy for all types of persons.

Two weighings in water serve to check the accuracy of the procedure, one at the completion of maximal inspiration and the other at the end of maximal expiration. The difference in weight obtained records hydrostatic displacement which serves as a measure of vital capacity. This determination of vital capacity when corrected for the effect of the mean hydrostatic pressure on thoracic volume gives values comparable to those obtained by the standard method employing spirometry.

The greatest error in the procedure arises from the determination of residual lung volume. If the variation in this measurement is of the order of 200 c.c., values for specific gravity will be subject to an error of $\pm$ 0·003. Repeated determination on the same individual permitting the use of a constant volume for residual air gives values that agree to within 0·003. A second error may arise from the presence of gas in the abdominal viscera. In an attempt to minimize this error, determinations should be made in the morning on the fasting individual.

In the same individual loss or gain of weight in response to a restricted or augmented diet is associated with an increase or decrease in specific gravity of the whole body. The density of the tissue lost or gained can be computed as 0·94, approximately that of fat. From these studies it appeared that there was a simple inverse correlation between the percentage of body fat in relation to total weight and the specific gravity.

The analyses of Rathbun and Pace [4] further established a remarkable quantitative relationship in guinea-pigs between fat content and specific gravity. This relationship, an inverse proportion, is expressed by the correlation coefficient $r = -0{\cdot}97$. These investigators found a range of values for specific gravity similar to those recorded for man, 1·021 to 1·096. The corresponding values for fat content as analysed of the guinea-pigs were 35·8% and 2%.

Uniformity of composition of the lean body mass.—If fat is the chief variable responsible for alterations in specific gravity of the body as a whole, then there must be a remarkable uniformity in the specific gravity of the lean body mass and hence, in the composition of this body mass. Table I indicates the agreement in percentages of water and organic nitrogen in the bodies of various mammalian species.

Measurement of body fat content based on determination of total body water.—If the percentage of water in the lean body mass is constant for healthy adults then it should be possible to estimate the fat content from the determination of total body water. Murray Steele and his co-workers, Messinger, Soberman, *et al.* [5, 6, 7], were able to make satisfactory total body water determinations in man based on the content of injected antipyrine in blood and body fluids. Employing the method of specific gravity as an *independent* estimate of fat content it was found that the percentage of water in the lean body mass was about 72. This is a fundamental value, which if constant for healthy adults, permits an accurate estimate of body fat according to the simple formula,

$$\% \text{ body fat} = \frac{100\,(72 - \% \text{ body water})}{72}$$

TABLE I.—SUMMARY OF MEAN WHOLE BODY WATER AND CHEMICALLY COMBINED NITROGEN CONTENT FOR ADULT MAMMALS

Species	Per cent water	Per cent nitrogen	Per cent fat	Per cent water in lean mass	Per cent nitrogen in lean mass
Rat	65·3	3·54	9·0	71·8	3·89
„	63·6	3·04	14·6	74·4	3·57
„	61·5	3·01	15·3	72·6	3·56
Guinea-pig ..	67·1	3·18	10·0	74·2	3·51
„ ..	63·5	3·08	12·3	72·4	3·52
Rabbit.. ..	69·2	2·91	7·8	73·5	3·09
„	74·3		2·5	76·3	
Cat	66·7	3·22	7·9	72·4	3·50
Dog	59·5		20·01	74·5	
„	59·1		15·4	69·9	
Monkey ..	68·5		6·5	73·3	
Mean				73·2	3·52

Table II gives results obtained for specific gravity and body water on a representative group of 88 adult males.

TABLE II.—RELATIONSHIP IN MAN OF BODY SPECIFIC GRAVITY, BODY FAT AND BODY WATER

Subject	Specific gravity	% Body fat		% Body water		% water of lean body mass
		From spec. gravity	From antipyrine	From spec. gravity	From antipyrine	
1	1·021	39·0	41·5	44·4	43·4	71
2	1·032	33·2	29·0	49·3	51·8	77
3	1·032	27·5	30·4	53·0	50·7	70
4	1·044	27·0	25·2	53·4	53·2	73
5	1·045	26·5	31·0	54·0	50·0	68
6	1·057	20·5	17·2	58·2	60·5	76
7	1·061	18·5	16·3	58·6	58·8	72
8	1·061	18·5	20·4	58·6	58·0	72
9	1·064	17·0	19·9	59·6	58·5	72

Concluding comment.—The concept that the mammalian body consists of a lean body mass of uniform composition is most fundamental and essential in the investigation of many physiological and clinical problems pertaining to metabolism, drug dosage, and muscular function. Since the excess fat content in normal individuals varies from 2 or 3% to 40%, all analytical results relating to body composition and formation must be expressed in terms not of total body weight but of *lean body mass.* Many more analyses are required to determine the percentage of bone and other components and constituents of the lean body mass but it can be inferred from the specific gravity data that not only is the percentage of body water constant, but also cellular water, extracellular water, protein, minerals, essential lipids, blood volume, and the percentage weight of various tissues and organs. Post-mortem analyses of the human body have been too limited as yet to afford reliable data but such analyses are necessary with particular care taken to determine the amount of essential lipid material. The "fat free" body as analysed post mortem by chemical methods is not the same as the lean body mass which is an actual *in vivo* entity which can be quantitated by specific gravity determinations. The procedure of specific gravity is not only applicable *in vivo* and post mortem but it serves to replace and perhaps to measure fat content more accurately than chemical analysis. It is necessary however to utilize both specific gravity and analytical chemical procedures to elucidate further the fundamental concept that healthy mammalian bodies are uniform in composition.

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Dr. E. M. Widdowson and Professor R. A. McCance: *Observations and Estimations of the Total Amount o Fat in the Body.*

A method which has recently been published (McCance and Widdowson, 1951, *Proc. Roy. Soc. B.*, **138**, 115) for determining the total amount of fat in the body was described, and results which have been obtained with it were shown.

Men and women of "normal" weight for height contained about 16–17% of fat. The thinnest healthy man investigated had only 7%. A fat woman weighing 25 st. contained over 60%, i.e. she had 15 st. of fat in her body, and the methods used showed that she had no more muscle than the thin man with which to carry this burden about.

When a fat person loses weight, the loss of weight was shown to be due almost entirely to a loss of fat, but when a person of normal weight becomes undernourished there is a loss of muscle as well as fat and at the same time an increase in the proportion of the body occupied by extracellular fluids. This was demonstrated by a study of the rehabilitation of German prisoners of war who had been released from Russian labour camps in 1946–47.

Dr. D. A. W. Edwards: *The Behaviour of Subcutaneous Fat in Lipodystrophy and Lipomatosis.*

Lipodystrophy and diffuse symmetrical lipomatosis are two examples of disorders of subcutaneous fat.

Lipodystrophy is characterized by symmetrical loss of subcutaneous fat from some part of the body, so that in the lipodystrophic areas the subcutaneous tissue layer is so thin that the outlines of the muscles can be clearly seen. The thickness of a fold of skin and subcutaneous tissue is much the same everywhere in these areas, being scarcely greater than that of a fold of the skin alone. This is in contrast to what is found in the normal thin person, where the folds, although thin, vary much more in thickness from place to place. There is clearly a loss of some tissue between the skin and the deep fascia in lipodystrophy. What tissue remains has been examined microscopically by several workers (Christiansen, 1922; Smith, 1921; Weber, 1920; Wells, 1940) who have all found a complete, or almost complete, absence of fat globules. Wells (1940) states that the cells which normally store fat are absent. In contrast to this, in an emaciated person the adipose tissue cells remain and they still contain a small globule of fat although their cytoplasm is reduced in volume. The evidence, therefore, suggests that in lipodystrophy there is a local disappearance of the fat storing cells rather than a local decrease in the amount of fat in each cell.

The opposite condition, diffuse symmetrical lipomatosis, is characterized by a symmetrical abnormal increase in the amount of subcutaneous fat in some part of the body. Microscopically the excess tissue is similar to normal fat without any obvious increase in the non-fatty constituents. Moreover, its response to changes in the total storage fat of the body is the same as normal fat. This can be shown quite simply in the following way. If an obese woman is put on a reducing diet, and, as she loses weight, the thickness of the fat is measured by the fold method, it is found that the thickness decreases at the same rate over the whole body. In other words, if the thickness of the fat at one place is halved, it is halved everywhere. The same thing happens in lipomatosis, so that when the thickness of the normal tissue is halved, the thickness of the area of lipomatosis is halved at the same time (Edwards, 1951*a*). Although normal parts of the body may in this way become quite slim or even very thin, the areas of lipomatosis remain abnormal in shape and plump in proportion to the rest of the body, because the pattern of distribution of the fat remains the same, however much total fat there is. When the normal parts of the body carry an average amount of fat a lipomatotic leg may not attract much attention or at least the disorder may not be diagnosed.

There are two interesting points about this excessive fat. Firstly, the thickness is nearly equal all the way down the limb as far as the wrist or ankle. This is in contrast to the normal pattern, in which the fat is much thicker at the proximal end of the limb than at the distal end. Secondly, this new pattern of distribution of the fat along the limb is very similar from one patient to another, so that the increase in thickness does not seem to be a random process, but occurs according to a fixed pattern, which is quite different from the normal distribution pattern (Edwards, 1951*a*).

Now this increase in fat might occur in either of two ways. There might be more fat in each cell, without any change in the number of cells. On the other hand, there might be more cells, each containing a normal amount of fat. The answer to this problem was obtained in the following way.

It has been found that subcutaneous fat cells from different places on the same person appear to contain about the same amount of fat, judging by the average size of the cavities in the cells seen in paraffin sections. Similarly, it has been found that if the average size of the cavities in fat cells from different people, but from the same place on the body, are compared, then the fatter the person is the more fat there is in each cell, and there is a simple proportional relationship between the thickness of the layer of subcutaneous fat at a given place, and the amount of fat in the cells (Edwards, 1951*b*).

Samples of abnormal tissue were obtained from the legs of two patients with lipomatosis, but unfortunately samples of normal tissue were not taken from them at the same time. The observations on normal tissue were therefore used to get a rough idea of what the cells of the patient's normal tissue would look like. This was done by measuring the thickness of fat in the normal areas of the patients, then finding cadavers with similar measurements.

When the cells of the abnormal tissue are compared with cells from normal tissue of the same or another region of a cadaver, of the same general build as the patient, the average size of the cavities in the various tissues appears to be very much the same, so that, because the thickness of the abnormal tissue is much greater than that of the normal, the difference in thickness must be due to a difference in the number of cells, since the amount of fat in the cells is the same.

Here, then, are two disorders of fat-storing tissue. In lipodystrophy there is apparently a local disappearance of the fat-storing cells, and in lipomatosis an increase in their number. In lipomatosis, once the new cells have been developed, they behave normally to changes in the amount of body fat and seem to contain the same amount of fat as the other subcutaneous tissue fat cells of the body. The two conditions seem to be disorders of numbers of fat cells rather than functions of fat cells.

But perhaps the most surprising observation of all is that both these disorders commonly occur together in the same patient.

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