OBESITY

ITS PATHOGENESIS, ETIOLOGY AND TREATMENT

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CRITIQUE OF THE CURRENT ENERGY THEORY OF OBESITY

The usual conception of obesity, particularly in the United States, is that it is always caused by an imbalance between intake and output of energy. "Exogenous or simple obesity is the result of maladjustments between food and exercise. Endogenous obesity is due to the lowered metabolism resulting from a disturbance in hypothalamic or endocrine functions, e. g., gonads, pituitary, or thyroid" (Best and Taylor,[1] page 981).

According to Means,[2] both the exogenous and the endogenous type of obesity are due to a simple disproportion between the intake of food and the energy requirement of the body. Endogenous obesity is endogenous merely in the sense that in the creation of such a disproportion a fall in the rate of oxidation in the body plays a role. A much greater proportion of obesity, however, is of the exogenous type. As a matter of fact, the ratio between total caloric intake and total caloric output is what counts. Persons who gain weight readily, even though they apparently do not eat to excess, are usually phlegmatic; they worry less, sleep either longer or more soundly and when at rest relax more completely than persons of the normal, or thin, type.

This conception of obesity has been substantiated chiefly by Newburgh and Johnston [3] and almost universally accepted on account of its promulgation by leading authorities; yet it is not satisfactory, for the following reasons:

1. As nobody is in doubt that the law of conservation of energy holds also for the animal body and as it is an established fact that any surplus of intake of energy as compared with its output leads to accumulation of

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1. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 2, Baltimore, Williams & Wilkins Company, 1939.

2. Means, J. H., in Cecil, R. L.: Textbook of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1937, p. 659.

3. Newburgh, L. H., and Johnston, M. W.: The Nature of Obesity, J. Clin. Investigation **8**:197, 1930; Endogenous Obesity: A Misconception, Ann. Int. Med. **3**:815, 1930.

fat in the body, obesity may be called the result of an imbalance between energy intake and energy output. Such a statement is a tautology rather than an explanation of the nature of obesity. Many authorities have emphasized the fact that normal persons must be protected against such an imbalance in some way; otherwise the majority would become obese. As a matter of fact, they are well protected. The automatic regulation of intake and output of energy is controlled rather precisely by a number of so-called general feelings, such as appetite, hunger, satiety and the desire for muscular activity or for its restriction, the last being due to fatigue, weakness or exhaustion. But it is not only this nervous regulatory mechanism which tends to maintain the body weight. The thyroid, as well, adapts its activity to the requirement; it restricts the production of hormone and herewith the oxidative processes in the body if an insufficient amount of food intake threatens the maintenance of the balance, and it functions in excess if overfeeding is going to increase unduly the body weight. This adaptative power characterizes the living organism as compared with a physicochemical machine.

2. If exogenous, or simple, obesity is defined as the result of maladjustment between food and exercise, then it requires a breakdown of the mentioned regulatory mechanism, which is represented by endogenous functions of the living body. In other words, an exogenous obesity is always an endogenous one also. I am very much in doubt whether it is possible to produce obesity artificially in a normal person. What may be produced by artificial overfeeding or artificial restriction of muscular activity is a temporary overweight but not a persisting obesity. If I may use this formula, the relation of such a temporary overweight to obesity is rather similar to the relation of a leukocytosis to a leukemia. The capacity and tolerance of the gastrointestinal tract and the automatic regulations of a normal organism will prevent the evolution of a true obesity. All minute calculations concerning the intake and output of energy hold only for a physicochemical machine—all other conditions being equal—but they fail to be applicable for definite conclusions to a living organism with a far developed adaptative power.

3. To attribute stoutness to an increased appetite resulting either from faulty habits of eating (von Noorden, Joslin, Lichtwitz, Labbé and others, cited by Bauer [4]) or from a hereditary abnormality (Wilder [5]) is not quite justified. Appetite is a general feeling serving the organism to build up the necessary quantity of body tissue and to maintain the

4. Bauer, J.: Endogene Fettsucht, Verhandl. d. deutsch. Gesellsch. f. Verdauungs- u. Stoffwechselkr. **9**:116, 1929.

5. Wilder, R. M.: (*a*) The Regulation of the Weight of the Body, Internat. Clin. **1**:30, 1932; (*b*) Disease of Metabolism: Review of Certain Recent Contributions, Arch. Int. Med. **61**:297 (Feb.) 1938.

body weight at an approximately equal level. It is the requirement of the organism, both quantitative and qualitative, which rules the appetite. Appetite for sodium chloride or for calcium, for instance, is influenced by the functional condition of the adrenal or the parathyroid glands, respectively, as Richter and Eckert [6] demonstrated in interesting animal experiments. Putnam, Benedict and Teel [7] produced typical acromegaly and gigantism in a young female dog by treating it for fourteen months with intraperitoneal injections of an extract of the anterior lobe of the beef pituitary containing the growth-promoting principle. The dog acquired a ravenous appetite, but no one is likely to assume that daily intraperitoneal injections of pituitary extract stimulated it. Every one will rather assume that the injections provoked a tendency toward increased proliferation of cells, leading to gigantism and acromegaly, and that this increased cellular activity required a greater amount of energy and in turn led to an unusual intake of foodstuffs. The increased appetite is therefore to be looked on as an interposed factor not directly influenced by the injections but indispensable for the realization of the gigantism and acromegaly which the growth-promoting substance finally produced.

Reed, Anderson and Mendel [8] found that rats treated with thyroxin lost weight in spite of eating almost double (12 Gm. of food daily as compared with 7 Gm. for the controls). Administration of thyroxin undoubtedly increased the appetite, not directly but by the adaptation of the organism to the increased requirement of food. Every physician with any experience knows that the changes of the basal metabolic rate produced by a pathologic alteration of the thyroid are not followed regularly by corresponding changes of the body weight because of the individually different capacity of adaptation of the appetite to the requirement.

Although the existence of a primarily ill trained or hereditarily abnormal appetite causing obesity hardly can be disproved, there is no positive proof of its existence either, and many facts to be discussed here later argue against the validity of such a hypothesis. It is just as possible that an increased appetite is the consequence of the tendency of the body to gain in weight and that it represents only a necessary

6. Richter, C. P.: Salt Taste Thresholds of Normal and Adrenalectomized Rats, Endocrinology **24**:367, 1939. Richter, C. P., and Eckert, J. F.: Mineral Appetite of Parathyroidectomized Rats, Am. J. M. Sc. **198**:9, 1939.

7. Putnam, T. J.; Benedict, E. B., and Teel, H. M.: Studies in Acromegaly: Experimental Canine Acromegaly, Produced by Injection of Anterior Lobe Pituitary Extract, Arch. Surg. **18**:1708 (April) 1929.

8. Reed, L. L.; Anderson, W. E., and Mendel, L. B.: Factors Influencing the Distribution and Character of Adipose Tissue in the Rat, J. Biol. Chem. **96**: 313, 1932.

means for the realization of such a tendency. This would be a complete analogy to the mechanism operating in artificial acromegaly which I have just discussed.

4. The same reasoning holds true for the decreased output of energy in many cases of obesity. The obvious restriction of muscular activity, the avoidance of any superfluous movement, the more or less marked laziness noted in many such cases may be the consequence rather than the cause of the overweight. Only infrequently do persons bedridden for some surgical reason, such as a fracture, acquire more than a slight and temporary overweight during the time of their inactivity. Such a forced restriction of muscular activity does not result in real obesity. An obese man who avoids unnecessary movements is behaving like a normal person who carries about a more or less heavy load. Thus the tendency toward a decreased output of energy is more the consequence than the cause of obesity.

5. Endogenous obesity is considered as an imbalance between intake and output of energy due to a lowered metabolism. Such a mechanism is possible and does not at all mean, as Wilder [5] claimed, that the law of conservation of energy fails to function. However, is this mechanism actually operating in cases of endogenous obesity?

(*a*) The simplest and most common explanation of the imbalance was formerly the assumption of a diminished basal metabolic rate in cases of endogenous obesity with a subsequently diminished energy requirement. No doubt a person with a lowered basal metabolic rate will increase his weight ceteris paribus, that is, if all other conditions remain unchanged. Increasing weight is therefore a frequent symptom in patients with hypothyroidism, and if it does not appear in all cases, it is because the status quo of other conditions is not maintained. Some few cases of obesity are to be explained by a lower basal metabolic rate, and in such cases overweight is actually one of the symptoms of hypothyroidism. In the majority of obese patients, however, one fails to detect a decreased basal metabolic rate and therefore a diminished requirement of foodstuffs.

I do not wish at this point to enter into a discussion of the difficulties of obtaining reliable values for the basal metabolic rate in obese persons but wish merely to emphasize the fact that in the great majority of such persons the rate has not been found to be diminished. In addition, one must recall the not infrequent cases in which even abnormal leanness is associated with a markedly diminished basal metabolic rate, as, for instance, in Simmonds' pituitary cachexia.

(*b*) When it became obvious that it was impossible to explain an apparent endogenous obesity by a diminished basal metabolic rate, an attempt was made to explain the imbalance on the basis of the not infre-

quent reduction of the specific dynamic action of food. If the intake of foodstuffs does not increase the oxidations, as under normal conditions, then, ceteris paribus, overweight must result. But, again, it is the balance of other factors which as a rule is disturbed by adaptative alterations of the body. Persons with a decrease in or practically an absence of the specific dynamic action of food are to be met with not only among the obese but also among the lean or even the cachectic. In addition, the possibility has to be emphasized that a diminished specific dynamic action could just as well be the consequence of obesity, for the reason that the transformation of carbohydrate into oxygen-poorer fat would not require any further intake of oxygen, and in this way the consumption of oxygen would be diminished.

(*c*) Efforts to prove a particular economy of muscular activity in obese persons (Gessler [9]) have failed. The working muscle of an obese person does not require less energy than that of a normal one.

A lowered metabolism has, therefore, not been proved to be the cause of endogenous obesity, except in those infrequent cases in which obesity is one of the symptoms of hypothyroidism. In those cases of endogenous obesity in which a disturbance of the functions of the hypothalamus, the gonads, the adrenal glands or the pituitary is apparently the cause of the endogenous obesity, a lowered metabolism has not been proved to be operating in the pathogenesis.

6. If a simple disproportion between the intake and the output of energy were the actual cause of obesity, then it would be necessary to discriminate between the different foodstuffs only as far as their caloric value is concerned. For the purpose of transformation of energy a calory is a calory; for the purpose of treating obese persons it is not. The experienced practitioner will reduce the intake of carbohydrates and fat but will not reduce the proteins to the same extent. On the contrary, an undue reduction of the protein calories will not only endanger the integrity of the cells but even inhibit a proper reduction of the body weight. It is not only the amount of calories but also the quality of equicaloric amounts of foodstuffs that counts.

7. Still another factor not to be explained from the point of view of a mere energy imbalance is the abnormal water and salt metabolism encountered, as a rule, in the more pronounced cases of obesity and lipomatosis (Zondek, Bauer [4]). Persons with such a metabolic disturbance frequently pass highly concentrated, scanty urine; a total amount of 300 to 500 cc. per day, with a specific gravity of 1.030 to 1.035, is not unusual. If they are given 1,000 to 1,500 cc. of water over a half-hour period, they usually show a marked retention; elimination does not take place in the normal time of four hours, but may be

9. Cited by Bauer.[4]

delayed twenty-four hours or longer (Volhard's test). If they are given 10 Gm. of sodium chloride, they usually retain the salt for two or three days, instead of eliminating it within the normal time of twenty-four hours.

My former co-worker dell'Acqua [10] determined simultaneously the sodium chloride content of capillary and of venous blood from thirty to one hundred and twenty minutes after the intake of 10 Gm. of sodium chloride in 125 Gm. of water. In some persons with uncomplicated obesity (6 among 13 examined), he found notably higher amounts of sodium chloride in the capillary than in the venous blood, the difference ranging from 40 to 15 mg. per hundred cubic centimeters. Similar differences have been encountered only in persons with certain types of renal lesions or with diabetes. The ingested sodium chloride is retained abnormally in the tissues.

Since the retention of sodium chloride and water in obese persons is not caused by impairment of renal function it must be due to an abnormal avidity of the tissues for these substances. That they are chiefly retained in the cutaneous and subcutaneous connective tissue seems probable from the studies of my former collaborator Recht.[11] The McClure-Aldrich test is a delicate indicator of the water content of the skin; the greater the content the more rapid are the resorption and disappearance of an intracutaneous wheal of a physiologic solution of sodium chloride. In a series of such tests Recht found a diminished resorption time in obese persons and also noted marked regional differences in the resorption time in persons with more localized lipomatosis. Those parts of the body surface containing larger amounts of fat showed a more rapid disappearance of the wheals. A dehydrating injection of a diuretic containing mercury, such as salyrgan, which in some cases is followed by a rapid loss of several pounds, was much less effective in the lipomatous regions of the body than in the others. In other words, the tendency of the subcutaneous connective tissue to accumulate larger amounts of fat is apparently associated with a tendency to store water in these particular regions of the skin. In some cases, Recht found the antidiuretic action of posterior pituitary U. S. P. to be unusually intensive and prolonged.

All these statements concerning the water and salt retention in obese persons have been completely confirmed by Wohl [12] in this country:

10. dell'Acqua, G.: Ueber Austauschvorgänge zwischen Blut und Geweben: die capillar-venöse Differenz des NaCl-Spiegels im Blute, Klin. Wchnschr. **8:** 1709, 1929.

11. Recht, G.: Ueber den Wassergehalt der Haut bei Fettsüchtigen: Untersuchungen mit der Quaddelprobe, Klin. Wchnschr. **8:**1748, 1929.

12. Wohl, M. G.: Metabolic Changes and Treatment of Obesity, Am. J. M. Sc. **183:**613, 1932.

namely, the retention in the Volhard test, the high water content of the skin as demonstrated by McClure and Aldrich's test and the difference in the levels of sodium chloride in the venous and the capillary blood after the administration of 10 Gm. of sodium chloride. Wohl found such differences as great as 100 mg.![13]

8. Hetherington and Weil [14] studied the chemical composition of the bodies of rats exhibiting pathologic obesity resulting from hypothalamic injuries. Calcium and phosphorus were considerably diminished and iron frequently diminished in percentage amounts as compared with values for the controls. They stated:

> It would seem that besides the obviously disordered fat metabolism in these cases of adiposity there is a more widespread upset of the body's physiological economy which takes in the calcium, phosphorus and iron exchanges, and possibly other factors as well.

The mere energy concept of obesity cannot account for these changes.

9. All the more does this hold true if the regional differences of fat deposition are considered. The difference in distribution of adipose tissue in both sexes does not need further discussion. In women rather well defined varieties of fat deposits are met with.[15] Most frequently, in about 90 per cent of all women, the distribution of fat is around the hips and on the thighs, the lower part of the abdomen, the buttocks and the back, as illustrated by Rubens' favorite subjects. One may therefore call this variety the "Rubens type." It corresponds to what is also called the "girdle type" of fat distribution. Other women show a particular accumulation of fatty tissue in the trochanteric region, which protrudes from the outline of the body. One may call this variety of obesity the "breeches" or the "trochanteric" type of fat distribution. Some women are annoyed by a more or less marked accumulation of fat in the lower extremities, usually extending from the hips to the knees or the ankles. In some women the excess fatty tissue is limited to the calves or ankles. In the more pronounced cases of this "inferior" type of fat distribution, the fatty masses are arranged like clusters and the skin on the surface of the thighs is subsequently covered with dimples. The opposite, or "superior" type of fat distribution is seen in women with relatively slender legs and abdomen and rather marked accumulation of fat in the back, the upper parts of the arms, the breasts, the neck

13. Wohl did not mention that his studies are merely a repetition and confirmation of the work done by dell'Acqua [10] and Recht [11] in my hospital in Vienna, although he was familiar with their work.

14. Hetherington, A. W., and Weil, A.: The Lipoid, Calcium, Phosphorus and Iron Content of Rats with Hypothalamic and Hypophyseal Damage, Endocrinology **26**:723, 1940.

15. Bauer, J.: Ueber Fettansatz, Klin. Wchnschr. **1**:1977, 1922.

and the face. Sometimes the unusual accumulation is limited to the breasts. As a matter of fact, there are also borderline conditions and combinations of these pure types.

The localized accumulations of fatty tissue are usually described as lipomatosis, but it must be understood that there are no sharp limits between a lipomatosis and a more or less generalized obesity. The mere fact that an abnormal accumulation of fat may show such different localizations must bring into the discussion of the pathogenesis of obesity another factor besides energy imbalance.

That the current, mere energy conception of obesity is unsatisfactory is a feeling expressed by several authorities in this country. Christian,[16] for instance, declared:

> We must acknowledge that in some cases of obesity the cause is obscure. To say that there is one essential cause, overeating, does not explain all cases . . .

In "Oxford Medicine," Howard and Mills[17] summarized their conception of obesity in the following words:

> In conclusion, it would seem that, although the immediate exciting causes of obesity appear to be the ingestion of abnormal amounts of food, or of alcohol, or deficient exercise, yet the underlying basis is probably an obscure endocrine dystrophy, which overthrows the weight-regulating mechanism of the body by an imposed economy of metabolism and consequently excessive storage of fat.

THE BIOLOGIC THEORY OF CONSTITUTIONAL OBESITY

1. *Lipophilia.*—Any satisfactory conception of obesity has, in my opinion, to consider first the unequal distribution of adipose tissue and consequently the variation in "lipophilia" of the subcutis in different parts of the body. In other words, a local factor must exist which influences the fat deposition in particular regions independently of the general energy balance or imbalance. The importance of such a local factor was first emphasized by Guenther (cited by Bauer[18]), who called the particular avidity to store fat "lipomatous tendency," or "lipophilia."

The enormous differences in lipophilia are obvious if one compares the cutaneous coverings on the forehead, fingers and lower part of the abdomen and back, even in the normal person. The lipophilia of a certain part of the skin tends to persist even when the skin is transplanted. Several observations in the literature[15] prove this point: Burns on the back of the hand in young girls, for instance, were treated by grafts taken from the lower part of the abdomen. Many years later, when the

16. Christian, H. A., in Osler, W.: The Principles and Practice of Medicine, revised by H. A. Christian, ed. 13, New York, D. Appleton-Century Company, Inc., 1938.

17. Howard, C. P., and Mills, E. S.: Obesity, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1940, vol. 4, pt. 1, p. 195.

18. Bauer (footnotes 4 and 15).

girls had grown and had acquired a certain degree of overweight, a second operation was necessary for the removal of the big fat pads which had developed in the grafted skin exactly as fatty tissue had developed in the skin of the lower part of the abdomen.

The frequently entirely unequal distribution of adipose tissue in obese persons demonstrates that a local factor must be also involved in the pathogenesis of obesity, whatever the cause of the condition may be.

The term lipophilia indicates a special tendency to deposit fat as well as a special resistance against the mobilization of fat from the adipose tissue. The existence of a different lipophilia in different regions of the body has been concluded from simple clinical evidence.[19] It exists whether or not its biochemical mechanism can be elucidated. Fortunately, its existence and involvement in cases of obesity can be substantiated by a number of facts.

Endeavors to demonstrate qualitative abnormalities in the metabolism of the obese subject have failed, according to Wilder's critical statement, in 1932.[5a] Contradictory results have been obtained by different authors who have studied the respiratory quotient (Arnoldi; Wang, Strouse and Saunders[20]; Hagedorn, Holten and Johansen[21]) and hunger lipemia (Kugelmann[22]; Hetényi[20]). Yet there have been found differences between obese and normal persons pointing toward an increased tendency of the former to store carbohydrates in the adipose tissue rather than glycogen in the liver and muscles. That carbohydrates are deposited in the adipose tissue in order to be transformed into glycogen first and then into fat has been proved by chemical and histochemical methods (Hoffmann and Wertheimer[9]; Loew and Krčma[23]; Richter[24]; Scoz, Baer and Boeri[25]). Von Bergmann and Goldner,[26] Kugelmann[22] and Brentano[27] have made statements suggest-

19. The experiments of Reed, Anderson and Mendel[8] showed that in rats such a local lipophilia has to be considered, too.

20. Cited by Wilder.[5]

21. Hagedorn, H. C.; Holten, C., and Johansen, A. H.: Pathology of Metabolism in Obesity, Arch. Int. Med. **40**:30 (July) 1927.

22. Kugelmann, B.: Untersuchungen zur Fettsucht als ein Problem intermediärer Stoffwechselstörung, Ztschr. f. klin. Med. **115**:454, 1931.

23. Loew, A., and Krčma, A.: Insulin und Nahrungsdepots, Biochem. Ztschr. **206**:360, 1929; Inselorgan und Fettstoffwechsel der Leber, Klin. Wchnschr. **11**: 584, 1932.

24. Richter, F.: Experimentelle Untersuchungen über das Vorkommen von Glykogen im Fettgewebe, Beitr. z. path. Anat. u. z. allg. Path. **86**:65, 1931.

25. Scoz, G.; Baer, P., and Boeri, E.: Insulina e ingrassamento, Arch. di sc. biol. **22**:142, 1936.

26. von Bergmann, G., and Goldner, M.: Funktionelle Pathologie, eine klinische Sammlung von Ergebnissen und Anschauungen einer Arbeitsrichtung, Berlin, Julius Springer, 1932.

27. Brentano, C.: Beitrag zur Physiologie und Pathologie des Ketonkörperstoffwechsels, Ztschr. f. klin. Med. **124**:237, 1933.

ing an abnormally low glycogen reserve in the liver and muscles of obese persons. Creatinuria, which Brentano stated to be an indication of glycogen mobilization in the muscles, is produced more easily and more rapidly in the obese than in the normal person by eliminating carbohydrate from the diet. Obese persons show a higher increase of lactic acid in the blood after slight muscular exercise than do normal persons, a fact which has also been confirmed by my former collaborator Medvei.[28]

Ketonemia and ketonuria depend on the relative proportions of fat and dextrose oxidized together, and more fat, as well as less dextrose, may account for ketosis. After a carbohydrate-free diet has been observed, the ingestion of olive oil increases the amount of ketone bodies in the blood of an obese person more markedly than in that of a normal one (Kugelmann[22]; Lauter and Neuenschwander-Lemmer[29]). This would indicate a lower rate of oxidation of dextrose together with that of the ingested fat in the obese persons.

On the other hand, there is some evidence of an increased stability of the fat deposits in obese persons as compared with those in normal persons. The fat stored in the adipose tissue in the former is not mobilized and made available for the organism so readily in case of need. My former collaborators Paschkis and Buttu[30] found that prolonged hyperventilation, as well as the oral ingestion of large amounts of alkali, both of which produce an alkalosis, raises the level of ketone bodies in the blood of normal persons, but that they are almost or entirely without this effect in obese persons. A ketonemia produced in such a manner is due to mobilization of fat deposits, which apparently, under the circumstances cited, does not take place so readily in obese as in normal persons. Under normal conditions creatinuria following glycogen mobilization in striated muscles, as in hunger, general anesthesia or various infections, is associated, according to Brentano, with a spontaneous endogenous rise of ketone bodies in the blood due to a mobilization of the fat deposits. Some obese persons, however, fail to react with a rise of ketone bodies in the blood during increased

28. Medvei, C. V.: Untersuchungen über den Kohlehydratstoffwechsel der Fettsüchtigen, Blutmilchsäure und Blutzucker bei der Arbeit, Ztschr. f. klin. Med. **122**:607, 1932.

29. Lauter, S., and Neuenschwander-Lemmer, N.: Ueber den Ketonkörpergehalt des Blutes bei Fettsüchtigen und Normalen, Ztschr. f. d. ges. exper. Med. **99**:745, 1936.

30. Paschkis, K., and Buttu, G. D.: Untersuchungen über die Hyperketonämie bei Hyperventilation und anderen alkalotischen Zuständen, Ztschr. f. klin. Med. **123**:764, 1933; Ueber die Ketonkörperbildung beim Fettsüchtigen. (Beitrag zur Pathologie des intermediären Stoffwechsels bei der Fettsucht), ibid. **123**:776, 1933.

creatinuria (Brentano[27]). MacKay and Sherrill[31] studied the ketonuria exhibited during a fasting period by both obese and normal persons. One group of the obese persons whose conditions were classified as endocrinopathies, but which I should call rather endogenous types of obesity, excreted appreciably less ketone bodies than normal persons. In the other group whose obesity was classified as "simple"—apparently of the "exogenous" variety—the ketonuria was as great as, and usually even greater than, in normal persons. MacKay and Sherrill concluded that the first group had some sort of "locked fat." In my own experience, obese persons do not exhibit ketonuria so readily as normal persons if put on a diet poor in carbohydrate.

Hetényi[32] reported experiments on obese subjects showing a markedly lower rise of the lipid level in the blood as compared with normal subjects if large amounts of fat were administered by mouth or subcutaneously or if artificial fever was produced. Even Wilder,[5b] who had been rather skeptical in 1932, stated in 1938, in commenting on these studies of Hetényi:

> These observations seem to indicate that mobilization of fat from fat depots is resisted in obesity and that deposition is accelerated. The condition seems analogous to the increased stability of deposits of glycogen in the liver and in the muscle in von Gierke's disease (glycogenosis). It seems to me that this conception deserves attentive consideration.

This conception is exactly the same as that which I[4] pronounced in 1929:

> Like a malignant tumor or like the fetus, the uterus or the breasts of a pregnant woman, the abnormal lipophilic tissue seizes on foodstuffs, even in the case of undernutrition. It maintains its stock, and may increase it independent of the requirements of the organism. A sort of anarchy exists; the adipose tissue lives for itself and does not fit into the precisely regulated management of the whole organism.

If I may put it somewhat exaggeratedly: A lipomatous subject may die of starvation and still remain lipomatous.

Finally, I want to mention that my former collaborator dell'Acqua[33] studied the amount of lipase present in the adipose tissue obtained from the living person during a surgical operation. The lipase content of the adipose tissue was found to be lower in obese than in normal persons and was lowest in the tissue of true lipomas.

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31. MacKay, E. M., and Sherrill, J. W.: A Comparison of the Ketosis Developed During Fasting by Obese Patients and Normal Subjects, Endocrinology **21**:677, 1937.

32. Hetényi, G.: Untersuchungen über die Entstehung der Fettsucht, Deutsches Arch. f. klin. Med. **179**:134, 1936.

33. dell'Acqua, G.: Ueber den Lipasegehalt des Fettgewebes bei Fettsucht und Lipom, Ztschr. f. d. ges. exper. Med. **71**:245, 1930.

From the foregoing statments it is evident that such an increased lipophilia is associated with an increased hydrophilia, that is, with an increased tendency to retain water and salt. This holds whether the abnormality is limited to particular regions of the body or is more or less generalized. An abnormally high hydrophilia may easily be tested and used as an indicator for an abnormally high lipophilia. This statement is of great practical value. Reduction of salt and fluid in the treatment of obesity is an essential point in my opinion, as in that of every one who has any experience in treating obese persons. It counteracts the manifestation of hydrophilia and, as it seems, therewith also that of lipophilia. In complete accordance with this view, Wohl [12] emphasized the importance of therapeutic dehydration, because thereby an obese subject "not only loses weight but is prevented from accumulating fat." [34]

It is conceivable that an abnormal "hydrolipophilia" may represent the primary disturbance resulting in an increased appetite and a subsequent imbalance between food intake and energy output, with a diminished specific dynamic action of food and even a lowering of the basal metabolic rate. It is the distribution of energy, too, that counts, not alone the rough imbalance between its intake and output.

It is erroneous to consider the adipose tissue merely as a passive storing place for fat and not to recognize that the adipose tissue as a part of the living body has, too, its own physiologic and pathologic processes.

What are the factors determining and influencing the lipophilia of the subcutaneous tissue? Three such factors must be assumed: an autonomous, an endocrine and a nervous.

(*a*) The Autonomous Factor: From the aforementioned facts, particularly from the results of skin grafts transplanted from the abdominal wall to the back of the hand, it is evident that any particular region of the skin has its own autonomous lipophilia which is a hereditary trait and characteristic of the particular region.[35] Physicians who are accustomed to study not only the patient but also his family will notice that identical or similar varieties of female fat distribution are found in other members of the family. The different varieties of fat distribution in women characterize the strain; they represent a hereditary, that is, a constitutional trait. Any such constitutional trait may, under certain

34. Best and Taylor,[1] in their excellent textbook, stated (page 982): "Undue restriction of the water intake is sometimes practised but this appears to be of no benefit and may be a detriment to health." Such a statement of physiologists is certainly not based on personal experience. In some fields clinicians have to teach the physiologists, and not, as usual, the contrary!

35. Bauer, J.: (*a*) Individual Constitution and Endocrine Glands, Endocrinology **8**:297, 1924; (*b*) footnote 15.

circumstances, become not only a familial but also a racial characteristic. The best example is what is called steatopygia in Bushmen, Hottentots and certain strains of sheep. The local accumulation of huge masses of adipose tissue in the buttocks represents an obvious racial characteristic. Sexual selection in man and artificial breeders' selection in sheep have transformed a formerly constitutional into a racial trait.

Hoffmann and Wertheimer [9] fed chiefly carbohydrates to dogs which had lost most of their fat during a previous period of starvation. They found an accumulation of glycogen in the adipose tissue, indicating the increasing storage of fat. Yet the glycogen was not equally distributed in all parts of the adipose tissue, but was found only in those places in which an actual accumulation of fat took place. In the adipose tissue of the orbits and of the soles, which remains practically unchanged during both starvation and fattening, no glycogen deposits could be observed. This experiment throws an interesting light on the autonomous regional differences of lipophilia, as well as on its biochemical nature.

(*b*) The Endocrine Factor: The most obvious influence on the regional lipophilia of the subcutaneous tissue is exerted by the testicles. The testicular hormone inhibits the accumulation of adipose tissue in those parts of the body which represent the chief sites for the accumulation in normal women, such as on the lower part of the abdomen, around the hips, at the breasts and thighs and on the back, where characteristic wide transversal folds of adipose tissue are found in the lateral parts. If the testicular hormone is lacking, the tendency toward accumulation of fat becomes obvious in those parts in which it is checked under normal conditions. Hence the female, or eunuchoid, type of distribution of adipose tissue occurs in castrated men or in those whose testicles have been destroyed by pathologic processes or have undergone atrophy on account of a primary lesion of the anterior lobe of the pituitary gland or of a definite hypothalamic center, or whose testicles were primarily hypoplastic and did not grow at the age of puberty ("eunuchoidism"). Hence, also, the regular female, or eunuchoid, type of fat distribution is present in obese boys in whom the physiologic production of the testicular hormone is not yet sufficient to prevent the accumulation of adipose tissue of the female type. The larger the quantity of fat deposited, the more striking is the resemblance to the female type and the more likely it may be erroneously considered as a sign of Fröhlich's dystrophia adiposogenitalis. This variety of prepuberal fat distribution might well be termed also the asexual, or sexually undifferentiated, type, since it is independent of sex hormones and is equally common in both sexes. Its presence at the prepuberal age by no means justifies the assumption of a gonadal or pituitary insufficiency.[36]

36. Bauer, J.: Common Diagnostic and Therapeutic Errors in the Management of Fat Boys, M. Rec. **151**:89, 1940; footnote 35*a*.

The ovaries have no influence on the regional distribution of adipose tissue.[35a] Castrated women do not differ from normal ones as far as the distribution of adipose tissue is concerned. What is frequently described as the hypogonadal variety of fat distribution, that is, the trochanteric deposit of fat pads, has no causal connection whatsoever with hypogonadism. Such a statement never has been substantiated and is simply copied by one author from another.

On the other hand, it cannot be denied, although hardly proved, that an insufficiency or absence of ovarian function may increase the general lipophilia under certain conditions. The mere energy concept cannot account for the obesity which develops immediately after castration or after the onset of any type of ovarian insufficiency. As a matter of fact, in only a moderate percentage of patients with such insufficiency does obesity actually develop. The ovaries have an influence on the hydrophilia, however. At the beginning of the menstrual period a tendency to retention of water and salt is found in normal women (Heilig[9]). During this time obese women gain in weight or do not respond to the dietetic restriction as they do before and after menstruation.

Insulin has been shown to enhance the deposition of carbohydrates in the adipose tissue (Hoffmann and Wertheimer[9]; Loew and Krčma[23]; Richter[24]; Scoz, Baer and Boeri[25]). This fact throws light on the nature of lipophilia and on the importance of considering the distribution of energy rather than merely the rough balance between intake and output. It is the intermediary metabolism which determines this distribution, and it is the intermediary metabolism which is obviously somewhat different in obese and in normal people. One part of the fattening effect of insulin injections on thin persons is to be attributed to the increased lipophilia of the adipose tissue.

The adrenal cortex has an influence on the lipophilia. The adiposity which occurs, together with other symptoms and signs, in cases of tumors of the adrenal cortex can by no means be explained by a simple imbalance between intake and output of energy; all the more if the characteristic accumulation of the adipose tissue in the face, the neck, the back and the upper part of the abdomen in contrast to the slender extremities is considered. It is a somewhat male type of fat distribution which is brought about in female persons with adrenal cortical tumors.

The pituitary gland has an indirect influence on lipophilia through the intermediation of both gonadal atrophy, in Fröhlich's syndrome, and adrenal cortical hyperactivity, in Cushing's syndrome.[37] It is, however, questionable whether or not the pituitary gland may influence directly

37. Bauer, J.: Was ist Cushing'sche Krankheit? Schweiz. med. Wchnschr. **66**:938, 1936.

the lipophilia of the tissues, as one is justified in doubting the existence of a pituitary type of obesity. Yet if obesity should prove to be caused directly by a functional alteration of the pituitary gland, then, again, only an altered lipophilia, and not merely an altered balance between energy intake and output, could account for its pathogenesis.

It may seem strange to doubt whether a pituitary type of obesity exists at all, when the textbooks and papers of clinical endocrinologists state it to be extremely common and correlate the girdle type of fat distribution with the pituitary origin of adiposity. Nobody has ever given a proof of the correctness of this view. The reason for such an erroneous conception is this: The great majority of women exhibit the girdle type of fat distribution, and the obesity of most of them cannot be proved to be of thyroid, gonadal or adrenal origin. As the authors do not realize any other possibility of explaining the nature of such obviously endogenous types of obesity, they make the diagnosis of pituitary obesity by exclusion without any positive evidence of an alteration of the pituitary gland. The more specialized in endocrinology a clinical writer is, the more dogmatic are usually his statements, and these are transmitted from one textbook or paper to generations of following ones.

(*c*) The Nervous Factor: The nerve supply of adipose tissue seems to regulate its lipophilia. If a peripheral nerve is severed or if other lesions of the peripheral nerves or of the spinal cord exist, an increased deposit of fat may result in those parts of the adipose tissue which get their nerve supply from the injured nerve tissue. Hausberger and Gujot [38] denervated the interscapular pad of brown adipose tissue in mice and rats and found that it rapidly increased in weight by accumulation of carbohydrate and fat. The brown adipose tissue was almost entirely transformed into the usual white or yellow adipose tissue, as the protoplasm of the cells was replaced by fat droplets. This statement has been amply confirmed.[39] In my medical department in Vienna, Adler-

38. Hausberger, F. X.: Ueber die nervöse Regulation des Fettstoffwechsels, Klin. Wchnschr. **14**:77, 1935. Hausberger, F. X., and Gujot, O.: Ueber die Veränderungen in Fett-, Wasser-, Glykogen- und Trockensubstanzgehalt im entnervten Fettgewebe, Arch. f. exper. Path. u. Pharmakol. **187**:655, 1937.

39. Cedrangolo, F.: Azione del sistema nervoso sul metabolismo dei lipidi di riserva, Arch. di sc. biol. **21**:570, 1935. Beznak, A., and Hasch, Z.: Effect of Sympathectomy on Fatty Deposit in Connective Tissue, Quart. J. Exper. Physiol. **27**:1, 1937. Kuré, K.; Oi, T., and Okinaka, S.: Beziehungen des Spinal-Parasympathicus zu der trophischen Innervation des Fettgewebes, Klin. Wchnschr. **16**: 1789, 1937. Bargi, L., and Politzer, M.: L'azione del ormone tiroideo sulla struttura istologica e chimica del tessuto adiposo innervato ed enervato, Rassegna di fisiopat. clin. e terap. **9**:613, 1937; Influenza dell'enervazione sulla struttura istologica e chimica del tessuto adiposo, ibid. **9**:554, 1937.

Mönnich and Tiberi [40] obtained the same results, and unpublished (because incomplete) experiments of Loebl and Hirschfeld seem to reveal a greater content of sodium chloride of the denervated fatty pad than that of the intact side. Diastase has been found in larger amounts on the denervated side (Hausberger [41]). Recent experiments seem to indicate that denervation of the intercapsular adipose tissue in white rats is followed by an increased tendency to deposit fat if a fat of a widely different iodine value is administered in large quantity after a period of starvation (Bauer, Nadler and Schwoner [42]).

These facts point toward an increased lipophilia as the operative factor in cases of so-called cerebral or hypothalamic obesity. Erdheim,[43] many years ago, came to the conclusion that when tumors of the pituitary gland were associated with obesity (dystrophia adiposogenitalis of Babinski and Fröhlich) the obesity was due to compression of certain cerebral centers on the floor of the third ventricle. Camus and Roussy,[44] as well as Bailey and Bremer,[45] confirmed this view on the basis of their animal experiments. Since epidemics of encephalitis have begun to occur, one occasionally meets with cases in which obesity develops as the result of inflammatory damage to these hypothalamic centers. Syphilitic or postvaccinal encephalitis, rheumatic chorea, tumors of the brain or hydrocephalus may produce obesity through the intermediation of a hypothalamic lesion. I observed extreme obesity develop in a young girl after scarlet fever associated with encephalitis. Definite evidence of the hypothalamic rather than of the pituitary origin of obesity occurring in cases of lesions around the hypophysial region has been given by the excellent work of Smith.[46] He succeeded in producing extreme adiposity in rats by experimentally injuring the tuber cinereum without involvement of the hypophysis. He failed, however, to obtain a similar result by removing or injuring the pituitary gland without involvement of the hypothalamic region.

40. Adler-Mönnich, J., and Tiberi, R.: Untersuchungen zur Biologie des Fettorgans, Wien. Arch. f. inn. Med. **30**:259, 1937.

41. Hausberger, F. X.: Ueber die Veränderung des Gehaltes an diastatischem Ferment im entnervten Fettgewebe, Ztschr. f. d. ges. exper. Med. **102**:169, 1937.

42. Bauer, J.; Nadler, S. B., and Schwoner, A. M.: The Effect of Nervous and Endocrine Influences upon the Fat Deposition in the Subcutaneous Adipose Tissue, to be published.

43. Erdheim, J.: Ueber Hypophysengangsgeschwülste und Hirncholesteatome, Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. (pt. 3) **113**:537, 1904.

44. Camus, J., and Roussy, G.: Experimental Researches on the Pituitary Body, Endocrinology **4**:507, 1920.

45. Bailey, P., and Bremer, F.: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921.

46. Smith, P. E.: Disabilities Caused by Hypophysectomy and Their Repair: Tuberal (Hypothalamic) Syndrome in Rat, J. A. M. A. **88**:158 (Jan. 15) 1927; Hypophysectomy and Replacement Therapy in Rat, Am. J. Anat. **45**:205, 1930.

Regarding the aforementioned facts, it seems justified to refer to an increased lipophilia of the adipose tissue as the chief cause of such a cerebral obesity. At all events, such a conception is better substantiated and more satisfactory than Wilder's [5] hypothesis explaining cerebral obesity by an abnormal irritability of centers of the diencephalon, where feelings of hunger and satiety originate. As I pointed out previously, these general feelings are adapted to the quantitative (energy) and qualitative requirements of the organism; they are under normal conditions, of course, ruled by this requirement.

2. *Definition of Obesity.*—I purposely did not try to give a definition of what may be called obesity until I had discussed the complicated matters leading to a better comprehension of the problem. I mentioned the difference between obesity and temporary overweight brought about by an induced imbalance between food intake and energy output. The German language permits a fine distinction between *Fettleibigkeit* and *Fettsucht*. The former defines an actual state of overweight, so to speak, a static condition of what may be called an excessive corpulence; the latter characterizes a dynamic tendency toward overweight. That is what I want to call obesity. Obesity may be defined as the compulsory tendency toward marked overweight due to abnormal accumulation of fat by persons who are left alone to their automatic regulations and are not supervised as far as the intake of food and expenditure of energy are concerned. The more localized such an abnormal accumulation of fat is, the more it is justified to call it lipomatosis rather than obesity. Yet there are no sharp limits between lipomatosis and obesity, as well as between obesity and the particularities of a lateral (pyknic) habitus which may still be considered normal. What has recently been described as "lipedema of the legs: a syndrome characterized by fat legs and orthostatic edema" (Allen and Hines [47]) is merely a not uncommon variety of such a hydrolipomatosis, which has been well known and studied for many years.[48]

Only the definition of obesity as I have given it suits the generally accepted conception of experienced clinicians who include obesity among metabolic diseases. Were obesity merely the result of a simple imbalance between intake and output of energy, it would not be justified to call it a metabolic disease. Corpulence of temporary character brought about by artificial overfeeding or artificial restriction of muscular exercise is not a metabolic disease.

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47. Allen, E. V., and Hines, E. A.: Lipedema of the Legs: A Syndrome Characterized by Fat Legs and Orthostatic Edema, Proc. Staff Meet., Mayo Clin. **15**: 184, 1940.

48. Bauer, J.: (*a*) Innere Sekretion, Berlin, Julius Springer, 1927; (*b*) Die Behandlung der Fettsucht, Klin. Wchnschr. **9**:2161, 1930.

3. *Etiologic Factors in Obesity.*—As I pointed out, there is no such thing as pure exogenous obesity. All obese patients must have at least a certain individual predisposition; that is, they must have a weight-regulating mechanism which is more readily overthrown than a normal one. All obesity is to a variable extent endogenous.

(*a*) Endocrine Obesity: There are cases in which obesity develops as a result of a tumor or other pathologic process in one of the endocrine glands. These cases justify the classification of hypothyroid, hypogonadal, adrenal and pituitary obesity. It is, however, a very small number of cases of obesity in which the condition may be classified as endocrine with full right. A critical analysis is necessary in order to declare an endocrine disturbance as the actual cause of obesity in a particular case.

Castrates and eunuchoids may be tall and slender as well as obese.[49] After the menopause only a moderate number of women, about 20 to 30 per cent, increase in weight. Estrogen or progesterone therapy has practically no influence on obesity. On the other hand, dietetic reduction of body weight without hormonal therapy may regulate a menstrual disorder. This experience has also been had by Wilder [5] and by Evans.[50]

Irregularity of the rhythm or intensity of menstruation, a late or premature onset or cessation of the menses, sterility, abnormality of the growth of hair, the presence of ovarian cysts and uterine fibromas, some diffuse or nodular enlargement of the thyroid and many other signs of abnormal endocrine function do not, in the majority of cases of obesity, indicate the cause of obesity but represent what I have called "endocrine stigmatization." [51] Obesity may have been present from early childhood, long before the abnormality of the ovarian function occurred. Hypertrichosis may persist unchanged after puberty and may be present in other members of the family who are not obese. The enlargement of the thyroid may not show any temporal connection with the onset of obesity and may not be associated with any functional disorder of the gland. Such an endocrine stigmatization therefore merely indicates some deviation in the glandular structure or activity and does not supply a sufficient explanation for a special glandular origin of the obesity.

(*b*) Cerebral Obesity: This variety is even rarer than endocrine obesity if diagnosis is based on undeniable facts, that is, on the evidence

49. Not all animal species gain in weight after castration.

50. Evans, F. A.: Nature of Obesity in Endocrine Disorders, Pennsylvania M. J. **42**:1174, 1939.

51. Bauer, J.: Die endokrin Stigmatisierten, Deutsche med. Wchnschr. **58**: 439, 1932; footnote 48*a*.

of a cerebral lesion being the cause of obesity in a particular case. In an analysis of 275 unselected cases of high grade obesity which I [4] published twelve years ago, there were only 2 instances of cerebral and 5 of endocrine adiposity. In all the rest of the 268 cases such a diagnosis could not be made.

(*c*) Constitutional Obesity: The term "constitutional" indicates any condition which is determined by the germ plasm, that is, any trait, either normal or pathologic, which is due to a particular gene or mendelian unit and is therefore hereditary. In the analysis of 275 cases, 73 per cent were found in which one or both of a patient's parents were obese too. If members of the family other than the parents were included, a hereditary factor was suggested in 88 per cent of the cases. These figures can be approximately confirmed from a material of at least 1,000 cases. The figures are significant even in full consideration of the great frequency of obesity. According to Carey,[52] it has been estimated that 1 of every 5 adults in the United States is overweight. Some authorities, for example, the physiologists Best and Taylor,[1] have claimed that the role of heredity in obesity is more apparent than real. Any experienced physician with open eyes knows that such a heredity cannot but be real (Wilder,[5] Gurney [53]). As a matter of fact, the constitutional character of the obesity in a particular case cannot be ruled out even if no other members of a patient's family can be found to be obese. This follows from the laws of heredity. I wish to stress the fact that in families affected with the hereditary trait of obesity, the condition is not exhibited by all members of the family. If, in spite of the same educational influence and the same environment, obesity develops in some members of a family and not in others, this is in full accordance with the laws of heredity. It does not, however, support the theory that particular habits arising from environment and education may account for an imbalance between food intake and energy output.

If any one were still in doubt whether or not obesity is really inherited, he would be convinced by the following two observations: Christiansen [54] described a family in which 2 sisters had 5 children each. Three and four, respectively, of the two sets of 5 children were rather big at birth. These babies, immediately after birth, displayed extraordinary appetites, grew very rapidly and accumulated prodigious amounts of fat. Only 1 of them survived the first year. Autopsy, performed in 1 case, did not reveal any explanation of the peculiar "macrosomia adiposa congenita," as the author termed the condition. This observation demon-

52. Carey, L. S.: Obesity, M. Clin. North America **23**:1449, 1939.

53. Gurney, R.: The Hereditary Factor in Obesity, Arch. Int. Med. **57**:557 (March) 1936.

54. Christiansen, T.: Macrosomia Adiposa Congenita: New Dysendocrine Syndrome of Familial Occurrence, Endocrinology **13**:149, 1929.

strated again that overfeeding is clearly not the real cause, but rather the compulsory consequence, of the pathologic anlage for obesity. Overfeeding is nothing but the means for the realization of the potentialities of this anlage.

Danforth [55] bred a strain of yellow mice presenting extreme obesity as a hereditary, dominant mendelian characteristic. Neither macroscopic nor microscopic examination revealed any abnormality to explain it. It is particularly interesting, in relation to Christiansen's observation, to note that in Danforth's strain of mice the pathologic anlage for obesity proved to be a so-called lethal factor if it was inherited from both parents, that is, if the mouse was a homozygote in respect to the character.

How does heredity operate to bring about obesity? Which anatomic structures or which functions does the hereditary factor affect? From the previous discussion it is clear that the gene or genes producing obesity do not affect one particular part of the body only, such as the thyroid, the pituitary or other endocrine gland, or some brain center which governs the accumulation of fat or is responsible for the general feelings regulating the balance of energy introduced into and spent by the body.

Without doubt the hereditary factor affects the local lipophilia of the tissues. This is proved by the previously mentioned familial type of regional accumulation of adipose tissue. I recall once more the steatopygia, which is a racial characteristic.

In addition, however, the anlage for obesity seems to operate also through the endocrine glands regulating the lipophilia and the metabolic conditions of the body. Such an assumption does not indicate a particular structural abnormality, an actual disease of one or several glands; it merely points to some functional alteration of the glands cooperating in the production of obesity. This is suggested by the frequent disturbance of various endocrine functions in obese persons and in members of their families. I discussed this fact previously and concluded that such an endocrine stigmatization is not to be looked on as the pathogenetic factor of obesity. It merely indicates some sort of biologic inferiority of the endocrine system.

It is not only a harmless state of endocrine stigmatization, however, which is met with in obese families. It is not exceptional to find a more serious alteration of some gland, such as a tumor, hypoplasia or atrophy, as the result of the biologic inferiority. I know several families in which constitutional obesity is present and in certain members of which tumors of the pituitary gland have developed at an advanced age. In these persons the obesity is not the result of the tumor; it is undoubtedly constitutional and has dated from early childhood. I also know obese families in which the members are obese one of whom is a eunuchoid.

55. Danforth, C. H.: Hereditary Adiposity in Mice, J. Heredity **18**:153, 1927.

In such a case the vicious cycle is obvious: The inherited constitutional obesity is the real cause of the biologic inferiority of the glandular system, and one of the glands became the particular victim of such an inferiority. Hypoplastic testicles may produce on their part the characteristic type of fat distribution and accumulation which is called eunuchoid obesity. In other words, a person with eunuchoid obesity may not be obese because of his gonadal hypoplasia but may display eunuchoidism as a result of a repercussion of the anlage for obesity on his gonads.

It fits well in the general pattern of the activities of genes and their relation to the phenotype if it is assumed that the genes causing obesity exert their influence not only on the local lipophilia of the adipose tissue but also on the endocrine glands and those centers of the central nervous system which regulate lipophilia and dominate metabolic functions, as well as those which are the site of the general feelings ruling the intake of food and the expenditure of energy. The analysis of the relations between the structure of the genotype and that of the phenotype is, in my opinion, the main task of constitutional physiology and pathology. The way in which the marvelous potential energies, represented by the genes and located in the chromosomes, bring about and rule the harmonic system of organs and functions of the living organism must be the chief objective of studies in the field of constitutional physiology and pathology. No matter whether or not this conception is entirely correct, one thing has to be kept in mind. It is that the definite body weight, the amount of adipose tissue deposited in the body, is determined by the germ plasm. The mass of the body as well as its height is determined by genes. All structures and functions involved in producing the mass and the height of the body seem to depend in some way on these genes.

4. *The Relations of Obesity to Other Constitutional Abnormalities.*— In considering an abnormal gene or gene complex as the cause of constitutional obesity, one must ask whether or not something is known about other genes related to the obesity anlage. First a negative statement can be made. The four blood groups have no relation to obesity.

Yet the hereditary factor which produces obesity may be associated with other abnormal hereditary characteristics and may represent in this way only one part of a more complicated abnormal constitutional syndrome. What has been described and discussed rather frequently in the last few years under the name of the Laurence-Moon-Bardet-Biedl syndrome is an association of obesity with polydactylism and syndactylism, retinitis pigmentosa, hypogenitalism, abnormalities of the skull (usually oxycephaly), deficient intelligence and occasionally other degenerative stigmas. Not all of the symptoms are met with in all cases, and a dissociation may be occasionally found in several members of one family.

I [56] have pointed out, as have my former collaborators Aschner [57] and Pool,[58] that the only satisfactory explanation of this peculiar syndrome is an alteration of several hereditary factors probably associated with each other by linkage of genes. This is a term used by geneticists for a persistent association of genes localized in the same chromosome, and therefore exposed more readily to a common alteration.

In a case under my own observation which was reported by Pool,[58] extreme familial obesity in a 12 year old girl was associated with polydactylism, syndactylism, hypophalangism due to an abnormal fusion of the phalanges, a marked congenital deformation of the skull, to be classified as acrocephaly, and intellectual disorders. This case represents a combination of two constitutional syndromes, the Bardet-Biedl and the Apert syndrome, which is called "acrocephalosyndactylism." At birth the girl had a weight of 6 Kg. (13.2 pounds). This fact justifies consideration of the adiposity as constitutional. It fits into Christiansen's [54] "macrosomia adiposa congenita." At the age of 12 years the weight was 182 Kg. (400 pounds) and the height 157 cm. Two brothers of the mother had a body weight of 160 Kg. (352 pounds) each; a third weighed 110 Kg. (242 pounds).

Another syndrome in which obesity is the leading symptom is the so-called Morgagni syndrome, which is characterized by the combination of obesity with a peculiar hyperostosis frontalis localized on the inner surface of the frontal bone and by some signs of virilism, such as hypertrichosis in women (Henschen [59]). I cannot agree with those authors who try to explain this syndrome as a pituitary or pluriglandular disorder. An association of several abnormal genes seems far more probable, in my opinion, as I have occasionally met frontal hyperostosis as a constitutional abnormality without any other pathologic condition. In some cases frank imbecility or psychoneurotic symptoms are associated with this syndrome, and rudimentary, as well as full blown, forms may be associated with an atypical set of symptoms belonging to the Bardet as well as to the Morgagni syndrome. This is in complete accord

56. Bauer, J.: Problems of Human Genetics, Bull. Johns Hopkins Hosp. **44:** 52, 1929; Constitutional Principles in Clinical Medicine, in Harvey Lectures, 1932-1933, Baltimore, Williams & Wilkins Company, 1934; footnotes 4 and 48*a*.

57. Aschner, B.: Zur Erbbiologie des Skelettsystems. Beiträge zur klinischen Konstitutionspathologie, Ztschr. f. d. ges. Anat. (pt. 1) **14:**129, 1928; Ueber die Arbeitsmethoden der menschlichen Erbforschung, Wien. klin. Wchnschr. **49:**1304, 1333 and 1362, 1936.

58. Pool, F. L.: Zur Entstehung genopathischer Syndrome (Bardet-Biedl-Akrokephalo-Syndaktylie), Wien. Arch. f. inn. Med. **31:**187, 1937.

59. Henschen, F.: Morgagnis Syndrom, Hyperostosis frontalis interna, Virilismus, Obesitas, in Aschoff, L.; Ceelen, W.; Koch, W., and Schürmann, P.: Veröffentlichungen aus der Konstitutions- und Wehrpathologie, Jena, Gustav Fischer, 1937, vol. 9, pt. 2.

with my explanation. Van Bogaert and Borremans [60] described a family whose members were affected with obesity, retinitis pigmentosa, brachydactylism and frontal hyperostosis. The irregular but frequent association of obesity with many different signs of a deviating constitution puts obesity among the other signs of what I have called "status degenerativus." [61] The term indicates an accumulation of many signs of a deviating, and therefore abnormal, constitution in one person.

In this same connection must be recalled the not infrequent association of obesity and biliary concretions, arteriosclerosis, diabetes and arterial hypertension. In the last two conditions the relationship to obesity is probably more intimate than one based merely on a common abnormal degenerative constitution. Hyperglycemia in obese persons frequently disappears after proper reduction of weight (Labbé [9]), and marked arterial hypertension in obese persons may be considerably lowered if the weight is reduced (Aschner [62]). Those are facts of great practical importance.

TREATMENT OF CONSTITUTIONAL OBESITY

Since as physicians we are unable to alter hereditary factors, it might seem that effective treatment of such an inherited constitutional condition as obesity would be impossible. Mendelian factors represent the unchangeable fate of a person, it is true, but we are still able to do a great deal for those whose inherited tendencies lead them to undesirable conditions. We may change the environment indispensable to the realization of the potentialities of the genes, and we may counteract their activity by interfering with the mechanism of the realization.

Many constitutional abnormalities exist which can be practically cured in spite of the impossibility of changing the underlying genes. Surgical procedures can repair polydactylism or syndactylism, a cleft palate and similar abnormalities. If a woman with black hair wishes to change this constitutional characteristic, she merely dyes it. On the other hand, she has to continue to dye it all her life if she wishes to hide it permanently, and the same reasoning holds true for the suppression of the anlage for obesity.

A normal person regulates his intake and output of energy automatically because of such general feelings as appetite and satiety and

60. van Bogaert, L., and Borremans, P.: La forme familiale de la rétinite pigmentaire avec cécité et obésité dite cérébrale (première observation anatomique), Ann. de méd. **39**:54, 1936.

61. Bauer, J.: Vorlesungen über allgemeine Konstitutions- und Vererbungslehre, ed. 2, Berlin, Julius Springer, 1923; Konstitutionelle Disposition zu inneren Krankheiten, ed. 3, ibid., 1924.

62. Aschner, B.: Beziehungen der Fettsucht zu arteriellem Hochdruck, Diabetes mellitus und Cholelithiasis, Ztschr. f. klin. Med. **116**:669, 1931.

because of his normal glandular and nervous functions. A person with a constitutional obesity which he wishes to suppress cannot rely on his automatic regulations and must follow a certain regimen which counteracts them. In other words, the obese person is forced to eat and drink not what he wants but what his physicians consider useful. He cannot rely on his automatic regulations if he wishes to avoid the consequences of his constitutional trait. We are fully aware of the fact that our treatment of obesity cannot be entirely satisfactory so long as we are not familiar with all the abnormalities of the pathologic intermediate metabolism and so long as we have no possible way of influencing the abnormal lipophilia of the fat-accumulating tissue. We can, however, inhibit the abnormal tendency by a number of means.

In no case should obesity be treated without the prescription, first of all, of a dietetic regimen. All other therapeutic procedures are secondary to this one. Not only a general quantitative reduction of calories should be instituted, but their quality should also be considered. Carbohydrates and fat are known to be likely to be deposited as fat, whereas proteins are more readily burned and utilized. They stimulate the thyroid activity and have the greatest specific dynamic action. This sort of fuel increases the flame in the stove more than any other variety.

On the basis of these facts, we put the patient on a diet containing about 1,100 calories, but no more than 20 to 30 Gm. of fat and 85 Gm. of carbohydrate. The rest of the diet consists of such proteins as lean meat, fish, cheese and eggs. I have sometimes had the rather paradoxic experience that patients whose general intake had been increased by the addition of protein calories lost in weight, whereas their former diet, although poorer in total calories, did not have this effect. Proteins in not too small amounts are indispensable in any case in which the body weight is to be reduced, in order to prevent the risk of damage to parenchymatous organs from chronic undernourishment.

It is necessary, too, to restrict the intake of salt to about 2 to 3 Gm. per day and to limit as far as possible the intake of fluids of all kinds. By this treatment alone all obese patients lose up to a certain point. There the weight becomes stationary, partly as the result of water retention.

At this stage thyroid should be given if no contraindication, such as marked tachycardia, cardiac insufficiency or a definite hyperthyroid state, prevents its use. It should be given regardless of the presence or absence of hypothyroid symptoms. It must act here not as a substitute for insufficient thyroid function but as a stimulant for the oxidative processes and the mobilization of water and salt from the tissues. The basal metabolic rate is of little or no value in deciding whether or not thyroid should be given. The general clinical picture, however, is decisive.

The duration and degree of thyroid treatment depend on the tolerance and reaction of the patient. Relatively high doses are advisable for four to six days, and the "thyroid push" should be repeated after several days of rest. This method seems more effective than the administration of small doses of thyroid continuously over long periods.

It is well known that many obese patients react to relatively mild thyroid treatment with tachycardia and increased nervous irritability, so that this therapy must be discontinued before the desired loss in weight has been produced. In such cases small, nontoxic doses of thyroid should be given in combination with intramuscular injections of a protein preparation. The simplest method is the injection of from 3 to 5 or 8 cc. of boiled milk every four to six days. Neither the thyroid nor the protein therapy in itself decreases the body weight; only the combination is effective. It seems that the protein injections determine the direction of the thyroid activity toward the metabolic processes, these being sensitized by the parenterally administered protein.

When the tendency to water retention is obvious, particularly if it is increasing, the use of a diuretic containing mercury, such as salyrgan or merbaphen, is indicated. The administration of the diuretic should be repeated as necessary at intervals of at least four to six days, and the effect can be markedly increased by the production of artificial acidosis through the oral administration of ammonium chloride, in doses of from 4 to 8 Gm. per day, for two or three days before and on the day of the injection of the mercury-containing diuretic. In many cases a "water push," that is, the intake of 1,000 to 1,500 cc. of water within fifteen to thirty minutes, may have the same dehydrating effect as the use of a diuretic. In spite of the delayed elimination of the liquid in hydrophilic obese persons, the exaggerated, though delayed, diuresis and the extrarenal loss of water may produce a considerable loss of weight after twenty-four to forty-eight hours. This method has been described by my former associate Aschner.[63] A similar underlying principle is employed in various spas in which saline waters are used to promote intestinal and renal elimination of water.

The output of energy should be increased as far as possible by the prescription of greater muscular activity, in the form of walking and other physical exercises, with due regard to the patient's cardiac state. Massage is indicated to loosen fatty masses, particularly when they are accumulated in certain regions of the body surface. This is the only, and unfortunately not a very satisfactory, way to determine the sites in which mobilization of fat should take place. Patients with hydrolipomatous legs should wear elastic stockings to prevent the accumulation of water. When huge masses of fat have accumulated, particularly in

63. Aschner, B.: Zur Therapie der Fettsucht, Klin. Wchnschr. **7**:2242, 1928.

the lower part of the abdomen, their surgical removal may sometimes be of great value, though surgical intervention should always be preceded and followed by appropriate general treatment.

The question whether glandular preparations other than thyroid should be used in the treatment of obesity is still widely discussed. My personal experience leads me to say that only estrogen preparations need be taken into consideration, and then only when ovarian insufficiency is clear. They may diminish the tendency toward water retention to a certain extent. They may aid in provoking menstruation when amenorrhea is present. But they have no effect on the obesity itself. The animal experiments of my former collaborators Adler-Mönnich and Tiberi [64] make it seem advisable not to prescribe thyroid and estrogen preparations at the same time, as the effect of the estrogen is checked by the thyroid. I have never seen any improvement in obesity from the use of preparations of the pituitary. The different combinations of glandular substances now available for clinical use are at the best superfluous; such effect as they produce is dependent on the thyroid substance which they contain.

Finally, but not of least importance, one point should be stressed: If the reduction in weight has reached a certain point and a further reduction seems impossible, treatment should be discontinued for several weeks, during which time the weight is kept unchanged by an appropriate diet. The resumption of treatment after this period often results in a further reduction of weight.

Once more I should like to emphasize the necessity of maintaining a dietetic regimen for a long period, if not for the patient's lifetime. His general feelings regulating the intake and output of energy eventually seem to adapt themselves to the prescribed regimen, so that, as a rule, the originally awkward compulsion becomes gradually a habit which is no longer troublesome.

SUMMARY

The current energy theory of obesity, which considers only an imbalance between intake of food and expenditure of energy, is unsatisfactory.

It is the distribution of energy in the body too which counts, not alone the rough imbalance between its intake and output.

The adipose tissue is not merely a passive storing place for reserve fat, but a living and active part of the body, with its own physiologic and pathologic processes.

The tendency of the adipose tissue to accumulate fat (lipophilia) varies widely in different parts of the body and also in different persons.

64. Adler-Mönnich, J., and Tiberi, R.: Zur Wechselbeziehung zwischen Schilddrüse und weiblichen Geschlechtsorganen, Wien. Arch. f. inn. Med. **32**:41, 1938.

Increased lipophilia is as a rule associated with increased hydrophilia (tendency to retain water and salt).

Lipophilia is determined and influenced by (*a*) an autonomous, (*b*) an endocrine and (*c*) a nervous factor.

There is some evidence that the adipose tissue of an obese person differs from that of a normal person inasmuch as it has greater lipophilia and resists more a mobilization of fat.

Obesity is defined as the compulsory tendency toward a marked overweight due to abnormal accumulation of fat by persons who are left alone to their automatic regulations and are not supervised as far as the intake of food and expenditure of energy are concerned.

While obesity is a definite metabolic disease, corpulence of temporary character brought about by artificial overfeeding or artificial restriction of muscular exercise is not.

The cause of obesity is in a very small number of cases an endocrine disturbance or an alteration of certain cerebral centers; in the vast majority of cases it is a particular constitution; that is, an abnormal gene or gene complex.

An increased appetite with a subsequent imbalance between intake and output of energy is the consequence of the abnormal anlage rather than the cause of obesity.

Some more or less typical combinations of the gene for obesity with genes for other abnormal traits are discussed, such as occur in Laurence-Moon-Bardet-Biedl, Apert and Morgagni syndromes.

The treatment of obesity is outlined. It must be chiefly dietetic.