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Etiology of obesity

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THE ETIOLOGY OF OBESITY

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INTRODUCTION

The high rate of incidence of obesity is readily apparent to even the laity. The degree of this condition may be disguised to some extent by cleverly worn clothes but a proper appreciation of the extensiveness can be effectively gained at the bathing beach. One needs but to observe the advertisements and note the endless devices calculated to gratify the patient and incidentally, the company.

It is a peculiarity existing in the mind of the laity, and perhaps to some extent among the medical profession, that these individuals would become obese despite any action on their part. These individuals invariably insist that they are not heavy eaters. Many become resigned to the belief that they are destined to become fat.

The main reason I chose obesity as a topic for a thesis was because of its high rate of incidence and its important relationship to the practice of medicine. The hazards of being overweight are very real and carry all possible serious complications. That these hazards are not fancied but real is attested to by the proven life insurance statistics. These statistics definitely prove the shortened life expectancy and

markedly increased disability from other diseases incidental to this state.

The more earlier onset may merely bring on embarrassment and humility, with a possible resulting inferiority complex state. Later the degenerative diseases are apt to be ushered in. More marked disabilities resulting are those of the circulatory, metabolic, and endocrine disorders. Diabetes, circulatory diseases, cardiorenal states, biliary, and arthritis, etc. are but a few of the more important complications which may ensue should failure of correction occur.

Dublin and Lotka have analyzed the influence of weight on the duration of life of 192,304 men aged 21 years or over, accepted for life insurance. The deaths per hundred thousand, age being disregarded, are given in the following table.

Table I.

Influence of Weight on Mortality; Deaths per Hundred Thousand Men Accepted for Insurance.

Weight	Deaths
Standard	844
Underweight, total	848
Overweight, total	1,111
Underweight, 5-14%	833
Underweight, 15-34%	913
Overweight, 5-14%	1,027
Overweight, 15-24%	1,215
Overweight, 25% or more	1,472

Table 2.

Influence of Overweight on Mortality In Persons Aged 45 to 50 Years.

Pounds Overweight	Increase in Death Rate Over Average %
10	8
20	18
30	28
40	45
50	56
60	67
70	81
80	116

Thus it will be seen that the penalty for being overweight is severe. Dublin and Lotka concluded that "the penalty of overweight is one-fourth to three-fourths excess in mortality." These studies become still more informative when they are related to age, since excessive weight carries a much greater risk in persons beyond 45 years of age than of an earlier age. This greater risk is strikingly shown in table 2.

The definition of obesity is somewhat difficult. Insurance companies have offered standard averages for a relation of weight to height. These standards, however,

cannot be applied accurately to individuals because of their failure to take into consideration bone and muscle structure which contribute significantly to weight. With the foregoing factors taken into account, and providing no edema exists, it may be assumed that excess weight is attributable to an excessive deposit of fat.

The commonly accepted definition of obesity is that condition in which the body contains an abnormally large amount of adipose tissue. This excessive fat may be evenly distributed or may be present to a much greater extent in some regions than others. When the accumulation is specifically localized to one or more discrete encapsulated masses, reference is made to "lipomatosis" in contradistinction to "obesity".

The standard tables for weight, based on age and height, are merely averages; and, since they include large numbers of obese, are excessive.

Ward (64) gives a rough rule for calculation of normal weight, as 110 lbs. in the male (female 10 lbs. less) for 5 ft. height; with the addition of 5½ lbs. for each inch above 5 ft. He also details an over-weight index arrived at by dividing the actual weight by the ideal weight.

Coombs (16) illustrates this disagreement by citing

the following examples: According to Wood a woman of 20 who is 65 inches in height should have a weight of 125 lbs. Lawrence calculates her ideal weight at 127 lbs. and the Metropolitan Life Insurance Company at 179 lbs.

Evans (19) states that there should be a gradual reduction in weight after the age of 35, averaging about one-fourth pound per year, since after this age there is a wasting of muscle mass and the maintenance of weight is due to adiposity. He allows for bony framework, depending upon the individual build.

Behnke, Feen and Welham (76) present a different method of determining the presence of obesity. They used the body weight divided by volume as an index. They feel that the comparatively low specific gravity of fat makes the measurement of specific gravity of the body mass valid for the estimation of fat content. Their method utilizes the essential measurement of body volume based on Archimedes principle.

In the final analysis in practice, the judgement of optimum weights should be an individual matter and rest on the clinical experience of the medical adviser. To render a more accurate diagnosis, there should be a thorough history and physical examination given. Attention should be given to the patient's age, height and

weight, the distribution of the fat deposits, the posture and character of bony framework. This examination in addition to the average tables should serve as a basis for determining ideal weight. We must remember that slight overweight in youth is desirable, but a slight underweight is desirable past the middle age group. During this latter period infectious diseases are apt to give way to degenerative diseases and become a primary cause of death.

Because of the widespread prevalence of obesity and the attendance of numerous complications incidental to this condition, we feel that its significance has been overlooked too frequently by the laity and practicing physicians. The most important principle in treatment is concerned with the determination and removal of the cause of that condition. This paper is therefore being written in an attempt to evaluate the scientific literature concerning the etiology of obesity in order to determine those factors which play a part in causing obesity.

HISTORY

Obesity is a disease known to man from time immemorial with numerous references made to it in the Bible. It is represented in personifications of indulgence and in mythological figures. The meaning of the word itself seems to have appeared in the English language in the early 17th century. Its origin is from the word "obesus". Gradually it acquired a meaning of "that which has eaten itself away", "that which has eaten itself fat", and finally it was occasionally used to indicate fatness, laziness or slothness.

It has been deduced that overeating, laziness and fatness have been associated together from Roman times.

Hippocrates noted that obesity was the harbinger of other diseases by saying that "Those who are uncommonly fat die more quickly than the lean".

Later physicians of antiquity, too, such as Celsus and Galen, attempted treatment against this condition. Galen had recognized corpulency beyond a certain point as a disease.

Through the Middle Ages up until recent times little progress was made in the knowledge and treatment of obesity, and correspondingly few contributions also appeared in the literature.

In the 19th century more information came to light. Dr. Harvey's recognition and treatment of the disease by nutritional restriction became widely known throughout England. The treatment became known under the name of his celebrated patient Banthing. His treatment was later introduced into Germany by Vogel and attained some note. It is stated that he was the first man of recent times to teach the world that obesity was a curable infliction. He was employed by St. Mary's hospital as an undertaker. So little was obesity considered a medical disease in those days that this undertaker took it on himself to address to the people "An open letter on Corpulence". In this letter he stated that he himself had lost "2.5 stone", and had been converted from a man who could not tie his own shoes or walk down stairs other than backwards, into a comfortable elderly gentleman. (William Wadd, 1816, 71)

Obesity was more common in the latter part of the 19th century than at present. A mild degree of corpulence was thought to be normal and was frequently used as a yardstick of an individual's prosperity.

CLASSIFICATION

Classification of obesity is a difficult matter. Variances in the origin and nature of obesity have led to efforts to classify it on a basis of etiology, in differences of etiology, and on a clinical basis. Regardless of the method used some confusion and uncertainty remain. Lyon (5) clearly illustrated this difficulty as early as 1910.

Since the period of Van Noorden, obesity has been customarily classified under two categories of exogenous and endogenous forms. No agreement has been reached as to the characteristic criteria of each group, and therefor it has proved of little value in practical diagnosis. In recent literature there has been a tendency to omit this classification altogether, and the physiological problem as to the fundamental origin of obesity, whether it is exogenous or endogenous still exists.

Exogenous or simple obesity has been defined as the abnormal accumulation of fat as the result of maladjustment between food and exercise (1). This classification does not recognize that a low basal metabolic rate as a factor in reducing the energy expenditure, that work is performed more economically, nor that the reduction in specific dynamic action of food is an important

influence in the production of simple obesity.

Endogenous obesity is that which is attributed to a lowered metabolism resulting from a disturbance in hypothalmic or endocrine function, notably, of the pituitary, thyroid, or gonads. This so-called endogenous obesity is commonly regarded as an entity in which the law of conservation of energy fails to function.

The following classification is advanced, therefore, with the attempt to encompass the most numerous and important types of obesity commonly encountered, recognizing, however, that other unimportant types may exist.

1. Exogenous or Simple
2. Endogenous
    Endocrinopathy
        A. Thyroid
        B. Pituitary
        C. Gonadal
        D. Pancreatic
        E. Adrenal
3. Localized Adiposity
4. Hereditary

BASAL METABOLISM

Some investigators have attempted to explain a possible cause for obesity on the grounds that the basal metabolic rate of the common or simple type of obesity was low or that work is carried on more economically.

Basal metabolic rate is that term applied to the heat production of a subject who, while being awake, approaches as closely as possible the condition of complete muscular and mental rest. Other conditions should ideally include room temperature of 20°C., refrainment of undue muscular exertion or fatiguing effort 24 hours previously as well as some time immediately before the test.

Conditions known to influence the basal metabolic rate are those such as age, sex, race, climate, habits, pregnancy, variations in barometric pressure, chemical substances, and various infectious processes.

Varying investigators have utilized both methods of determining basal metabolic rate as by direct and indirect calorimetry. Later investigators have compared their findings with the established normal standards of individuals of the same sex and age, having normal weight and surface area.

Earlier investigators found that this energy expenditure was less at rest than normal. Critics hold that had they made a comparison on the basis of height they would have found just the opposite results. Investigations have since then demonstrated, however, that the basal heat production is proportional to the surface area of the body.

Boothby and Sandiford (13) measured the basal heat production of 94 obese subjects. They found that in 81 per cent of them the rates were within 10 per cent of the predicted heat production per square meter.

Warner and Weir (66) in their experiments on 21 patients obtained the following results: 10 patients were between 0 and 10 per cent, 4 patients between 11 and 14 per cent, and 7 patients between 0 and -10 per cent. All are within the standard limits of normal excepting four who were slightly above normal.

Preble (50) and his associates in a total of 39 cases found 7 over 10 per cent, 4 over 15 per cent, 4 over -10 per cent, and 1 over -15 per cent. It is thus seen that 21 were slightly above normal and 18 slightly below with variations about equal each way justifiably for them to call normal.

Strause and Dye (60) compared basal metabolic

rates of normal persons with those of subjects being underweight and overweight. Their results per square meter of body surface found relatively no differences.

Short and Johnston (55) made a study of 99 overweight patients with a range from normal to 135 per cent above normal. They made a study with regards to surface area, basal metabolism, total heat production, pulse rate, and blood and pulse pressure. Their results showed a progressive increase in total metabolism with an increasing percentage of weight with a slight tendency for an increase in the basal metabolism. Their results suggest a possible relationship to an increased thyroid activity as being the cause for this slight tendency toward an increased rate. The basis of their beliefs resulted from a study of the pulse rate in those cases presenting a resting rate over 80 in which the subjects were definitely more overweight than those having lower rates, and that the total metabolism was correspondingly higher.

Strouse and Dye (60) attempted to ascertain the cause or causes of what they termed "unexplained" obesity. They felt that metabolically speaking, the "constitutional" obese and the healthy underweight may represent extremes of the same problem. Their 4 cases

presented tend to bear out their argument by the subjects maintaining their weight. Criticism, however, is that these cases were maintained on a diet for less than one month and that water replacement could possibly have occurred.

Rony (47) agreed with the earlier and previously mentioned investigators that in the majority of obese cases the basal metabolism was essentially normal. He feels the majority of obese individuals present a variation of ±10 per cent but that this is also the range for the normal. In his number of 50 unselected cases of obesity observed in their clinic, the following study revealed: 31 cases having a basal metabolic rate within ±10 per cent, 4 cases between -10 per cent and -20 per cent, and 3 cases below -20 per cent, 8 cases between +10 per cent and +20 per cent. His observations, however, bring out one fact that compared with corresponding subjects of normal average weight, the total calorie production under basal conditions was greater in all but one of the obese patients. This finding however is not new. Both Lusk and Lauter brought this out. Several investigators have attributed this to the metabolism of excess fat tissue. Rony feels in addition, that interstitial structures, increase in cardiac work, and respiratory muscles, or in some cases due to a

latent hyper-thyroidism, may cause an increased total basal metabolism of the basic tissues in obese and normal weight persons. The previously mentioned factors would have to be eliminated or allowances made in some fashion or another. This task may be one which cannot be performed with satisfactory accuracy.

SPECIFIC DYNAMIC ACTION

Ingestion of food increases the heat production and this increase in heat production above the basal rate is called the specific dynamic action. Its effects are attained within a range of a few minutes to several hours after consumption of food. Maximum production being within about the third hour and maintained at this level for several hours. This increased heat production may result in an elevation of the basal metabolism from 8 to 25 per cent. The greatest specific dynamic action is exerted by protein food. Recent theories seem to favor deamination of the amino acids with a resultant formation of urea, as being the causative factors here. One observer estimates that carbohydrate causes a rise of about 6 per cent with that of fat being about 4 per cent.

This theory held that food materials were not metabolized in the same way by all persons and therefore implied that individual variations existed in the so-called specific dynamic action. In the attempt to demonstrate that this response was not caused by the digestive or absorptive processes, glucose and some of the amino acids were injected intravenously with a resultant production of an equally great reaction.

Some investigators feel that should some metabolic

fault prevent or greatly lessen this specific response to food there would be a gain in weight, provided the usual type and amount of food was consumed and that activity was not increased.

Reports from some observers such as Bauman (5), Mason (42), Plaut (48), and Wang, Strouse and Saunders (63) suggest a definite relationship between obesity and an abnormality in the specific dynamic action of food. Plaut perhaps produced the first notable investigation of specific dynamic action in a variety of cases and determined his own "normals". His investigation covered a series of normal and abnormal persons utilizing a mixed meal. The accompanying table illustrates some of this author's results.

Specific Dynamic Action of Mixed Meal

	No. Cases	Per cent increase
Normal persons	19	20 - 50
Constitutional obesity	12	4 - 29
Hypophyseal obesity	10	3 - 18
"Constitutional thinnes"	3	63,40,48 respect.

Results illustrate Plaut's findings of a very definite lowering of specific dynamic action of food in obese and a marked rise in opposite types of individuals, those

with so-called "constitutional thinness".

Wang, Strouse and Sanders (63) likewise hoped to find similar differences in the use of food by obese. Twenty-six tests were made on obese subjects using protein meals with eleven subjects, carbohydrate meals with eleven, and fat meals with four. The individuals varied in weight from 37 per cent to 140 per cent above normal and ranged in age from 12.5 to 34 years. In addition, tests were made on five apparently normal underweight subjects, ranging in age from 21 to 42 years, and in weight from 22 to 31 per cent below normal. Six tests with protein meal, three with carbohydrate meal, and two with fat meal were made. The five normal subjects varied in weight from +3 to -7 per cent from normal, and ranged in ages from 21 to 24 years. Meals used were six with protein meal, three with carbohydrate meal, and three with fat meal. Results with protein meals in obese showed a very slight increase in specific dynamic action. Thin and normal people showed a very high specific dynamic action of protein with the latter to a less degree. With carbohydrate meals normal subjects showed the greatest specific dynamic action, whereas obese subjects showed a lesser response. With fat meals, little, if any, specific dynamic action

manifested itself. This seems to follow in line with the previously mentioned investigators.

Mason (42) found a definitely increased percentage of specific dynamic action in thin subjects which he felt to be an important factor in the etiology of this condition.

The foregoing investigators represent, perhaps, the foremost proponents for one of the possible cases for obesity but they are held with issue at many points by the results of other investigators. Plaut has been criticized on various aspects, notably, regarding the shortened time element of his experiments with a resultant decrease in true results. Plaut's experiments lasted 4 hours or less. Strange and McCuggage (59) show that while the principle effect of a meal is manifest within the first 4 hours, approximately one-third the total heat production occurs in the second 4 hour period.

Benedict and Carpenter (7) found the specific dynamic effect in several instances as low as 3 per cent and as high as 33 per cent.

Lauter (41) made careful tests on obese persons and also found that the specific dynamic effect of foods varies just as widely in the obese as in the

normal. Rony questioned the frequency which specific dynamic action may be abnormally low in most cases of obesity. He further questioned its etiology when present. He thought it reasonable to expect that a large test meal consumed by such persons would stimulate their basal metabolism to less extent than a similar meal ingested by normal weight persons with moderate eating habits. In these cases, he felt, the low specific dynamic effect may not be a primary characteristic, but merely one of the consequences of overeating.

Test meals used by previous workers had been extremely varied. These ranged from moderate amounts of lean beef alone, or accompanied by bread. In addition to a great variety of meals having been used, variations in amount have also occurred which prevented comparison of their obtained heat results.

Wang, Strouse, and Saunders (63) record variations of protein intake between 32 and 66 gm. In addition, average protein ingestion by the obese and thin series was less than one-third and one-fourth, respectively than the normal series. One would feel that the cumulative effect of successive increases in protein intake necessarily enters here. Identical test meals

may, perhaps, be the solution here.

Hawk (28) introduces the question of whether sufficient time for complete digestion and absorption of the meal is present. He has questioned the typical time limit from 2 to 4 hours used by many previous investigators as being inadequate. The psychic factor with regards to proteolytic and enzyme secretion and digestion is also held to be variable and may be of importance with regards to independent heat production.

Base lines for the curves are frequently found in observers to be inaccurate for the true interpretation of their test results. The basal values taken immediately prior to the ingestion of food appeared to be the logical and most satisfactory method for studying small changes in metabolism noted immediately after taking of food. Percentage of specific dynamic action is held to be rather inadequate in that the word percentage is too vague and varies considerably. Ratios are failed to be clearly defined either in terms of body surface involved or the timing of their values, such as the maximum or total heat production. It appears that the basal line is also subject to further variations by such factors as age, sex, surface, and have no relationship with heat produced by standard test meal.

Strang and McCluggage feel that though apparent confirmatory evidences are obtained by some investigators in support of their lessened specific dynamic action in obese, the percentages are essentially comparable when similar values are used. They felt previous findings were the results of technique or interpretation. They attempted correction of all these factors. In their experiment they supplied the meal in an appetizing form, minimizing emotional stress. Components of each meal were weighed to 0.1 gram and consumed by patient in less than 20 minutes. Base line values determined immediately prior to ingestion of food. Basal test was made 14 to 16 hours after insuring a true post-operative state. Subjects were also given training regarding taking of basal metabolic tests. They arrived at contrasting results and obtained no significant difference in heat reaction to food in either mild or severe grades of obesity as compared to normal. Their tests also included several of the alleged types of obesity. Subjects represented by their tests included both sexes, young and old, varying graduations of obese, and ideal and thin weights, as well as an example of hypopituitary and acromegaly. They felt, however, that though they

found no heat reaction to food, their data provided no index of the physiological response of the subject to this extra heat. They felt that this change of heat production was of such magnitude as to produce abrupt alterations in the existing physiological status. These abrupt alterations in turn, would necessitate automatic adjustments in circulation, and temperature, etc., which could be greater than that particular individual's make-up could safely handle. This abrupt rather than the maximum rate of change of heat production is stressed as providing the source of physiological strain. Strang and McCluggage (59) found that identical meals produced the same total heat of reaction in normal, thin, and obese persons, but that the physiological load was approximately one-fourth less in the obese and one-fourth greater in the thin than the normal. Greatest increase in heat production occurs relatively earlier during meal in thin and normal individuals. In the obese this is not true but is characterized by a delay until about the second hour. These investigators point out that perhaps here lies the basis why fat people unwittingly eat large meals and remain fat and thin people correspondingly eat small meals and remain thin. They feel there is

a possible relationship between the degree of satiety and the physiological stress resulting from specific dynamic action of food.

LUXUSCONSUMPTION

Luxusconsumption deals with the theory that prolonged overfeeding increases the basal metabolism of individuals and that the failure of this response by the body results in an obese state. Some investigators, notably Grafe, have attempted to prove that this is a normal response in both dogs and humans. He supported his belief by comparing the metabolic rate of an overfed dog with its previous state of starvation. This greatly discussed experiment showed a progressive increase in the metabolic rate out of proportion to the increase in other investigator. Later investigators since then have revealed the fallacy of his observations. They point out the fallacy of accepting the metabolic rate following a period of prolonged starvation as an improper basis for comparison.

Experiments by other investigators have since shown that undernourishment produces a depression of the metabolic rate. Lusk (39) particularly brought this out.

Johnston and Maroney (33) made an interesting experiment in a number of apparently normal children aged 4 to 14 years. Their investigations show that only with large amounts of protein was comparatively

little change in basal metabolism produced. Results indicate, therefore, that mere caloric overfeeding is insufficient to produce an increase in basal metabolism and that excessive proteins are necessary.

Benedict, Miles, Roth and Smith further demonstrate that the heat production in the basal state falls as great as 30 per cent due to prolonged starvation. They fed a group of men who were habitually ingesting 3,200 to 3,600 calories with a diet containing only 1,400 calories. After three weeks the average weight of the subjects had declined 12 per cent and their basal metabolism had fallen 18 per cent. They were not able to maintain this new low weight on 1,950 calories and the basal metabolism remained low. They point out that the organism can reduce its rate of oxidation in response to underfeeding and, if the latter is not too extreme, weight may be maintained after an initial loss. The inference is of an adaptation capable of prolonging the life of an organism with undernutrition. They point out, however, on the other hand, that it is not easy to picture any advantage obtainable through the ability to dispose of an excess amount of food rather than to store it so that it would not be available in time of need.

Wiley and Newburgh (68) attempted to bear out

Grafe's results by studying the responses of a very thin person. They found no evidence of either a basal or total metabolism stimulated by excessive feeding. On the other hand the subject did add about 4.5 kilograms to his weight in 15 days. Results, therefore, do not confirm Grafe's findings.

It is apparent that the body does possess a mechanism that inhibits destruction of the body tissues when starvation is imminent. But this mechanism does not necessarily hold that the lean organism is so because it overoxidizes an otherwise adequate supply of food.

FAT METABOLISM

Hetenyi was one of the earlier and more important investigators regarding fat metabolism. He was led to believe that some local influences rather than general influences alone were responsible for obesity. His experiment suggestive of this (30) involved feeding 10 normal and 8 obese people on an insufficient diet. He obtained unchanged lipid levels in the blood of the normal individuals, whereas in the obese, a fall from 18 to 43 per cent had occurred by the end of the period. It was Heteny's belief that in normal individuals tissues gave up fat as rapidly as needed, thereby maintaining normal lipid levels in blood stream. In obese patients, however, a delay or hindrance in the release of fat was obtained. His experiments further included feeding large amounts of olive oil to obese and normal persons. Findings were an abrupt rise in fat levels in the normal individuals and a slight rise in the obese. He thought this indicated a more rapid deposit of fat in the tissues of the obese. He further injected 50 cc of olive oil subcutaneously and found an increase of the blood lipid levels from 10 to 48 per cent in the normals while in the obese the rise was only from 1 to 8 per cent. His belief was, therefore, that storage

is more prompt in obese and released less readily when once stored.

Hagedorn, Holt, and Johansen (27) found that obese subjects have lower post-absorptive respiratory quotients after two days of a diet consisting chiefly of carbohydrates than normals. They believed this was due to excessive conversion of carbohydrates into fat. They felt that perhaps an increased transformation of carbohydrates into fat or decreased utilization of ingested fat by the obese may be one of the methods the "body fat regulating mechanism" uses in increasing body fat.

Rony (46) later interprets this phenomenon as an earlier process of transforming glucose into fat. He feels that this process occurs while glucose is in the bowel so that no glucose remains for fat synthesis in the post-absorptive state.

Strause, Wang, and Saunders, (61) however, differ since they found no difference in the utilization of carbohydrates during the absorption of a carbohydrate meal in obese and non-obese subjects.

Kugelman (37) showed that there is a disturbance of the intermediary metabolism in these cases. The results of their investigations indicate that the fatty

tissue of the constitutionally obese possesses to a marked degree the ability to take up carbohydrates from the blood stream and transform it into fat.

Lauter, Neuenschwander and Lemmer (40) were, however, unable to confirm these observations by Kugelman of this lipomatous tendency. They reported that fat persons responded to feeding with fat oil with a higher than normal concentration of acetone bodies in the blood.

Kugelman (37) found the liver and the muscle to be relatively poor in glycogen indicating that the storage of this substance was prevented by the rapid extraction of carbohydrate from the blood stream by the fat cells.

McKay and Sherrill, (43) however, found evidence for the concept that in some cases the stored fat is less available for oxidation. They studied the ketonuria during the fasting of 11 obese and 5 normal subjects for a period of 5 days. 4 of the subjects classified as endocrinopathic excreted appreciably less ketone in grams per square meter of body surface than did normal subjects. The remainder of overweight persons who were classed as simple obesity the excretion was as great or greater than the normal subjects. They

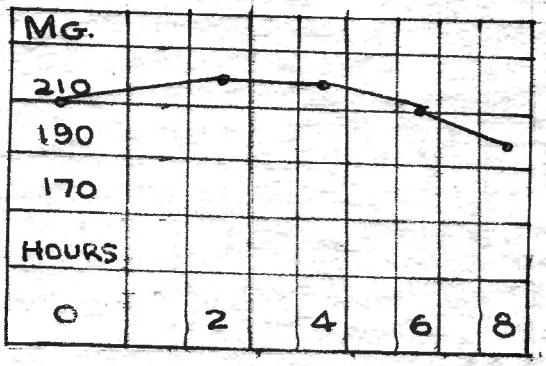
felt justified then in advancing the idea that "locked fat" was the result of some endocrine disturbance.

Goldzieher (24) summarizes the results of rather recent research by Hoffmann and Wertheimer on the response of the fat tissue to feeding. Their investigations showed that there is in the fat cells of the omentum and subcutaneous tissue of experimental animals within two hours after the intake of carbohydrates, an accumulation of up to 6 per cent of glycogen which disappears but gradually, either by transformation into fat or by release into the circulation in the form of glucose. The storage and gradual release of glycogen in the fat tissue is particularly significant with respect to the alimentary hyperglycemia which is so often met with in obese and diagnosed as diabetes. Hoffman states, "In reality, it seems to express the inability of the overcrowded fat tissue to fulfill its function as a reservoir of carbohydrates."

Blotner (11) made alimentary fat tolerance tests upon a number of thin, normal, and obese individuals. He used plasma cholesterol as an indicator of the blood fat concentration, and as a test meal, 500 cc of 20 per cent cream. The following charts made by Blotner illustrate the responses of all groups with a notable

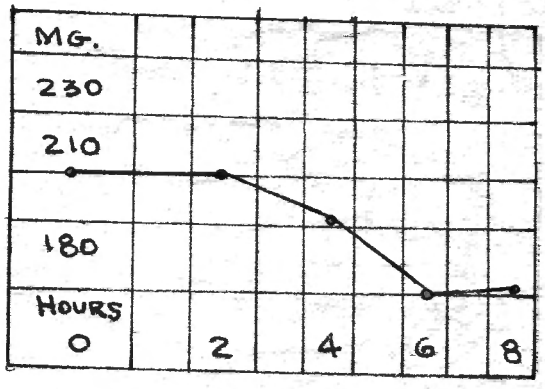
rise in the obese types.

Chart 1.



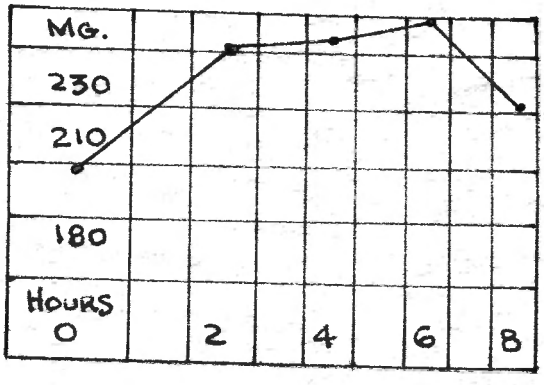
Average cholesterol curve obtained in 13 normal persons.

Chart 2.



Average plasma cholesterol curves obtained in 16 thin people.

Chart 3.



Average plasma cholesterol curves obtained in 21 obese persons.

LIPOPHILIA

Von Bergmann was the first to advance the theory of lipophilia. He hald that the tissues evidenced a lipophilic tendency resulting in a rapid deposition of fat in the body stores from which withdrawal was difficult. Wilder and Hetenyi both believed that a rapid withdrawal of fat from the blood occurs in the obese creating a demand for readily available energy acting to increase hunger, particularly for carbohydrates.

The only experimental data to support Bergmann's concept was supplied by Hetenyi (30). Heteny found that the total blood lipids of obese subjects decreased during undernutrition but remained constant in individuals of normal weight. Hetenyi interpreted, therefore, that the fat could not be mobilized for heat production. This was felt to be direct evidence that lipophilia actually was the determining factor in causing obesity. In each instance his subject lost at least one kilo of body weight during this period of undernutrition. It is felt that his interpretation could have been readily evaluated by nitrogen balance studies, but no such data was published. His experiments involved comparison of levels of blood fat in obese persons with those of normal persons when the usual food was taken and again after

eight days of restricted diet. The following table gives his findings:

Blood Levels of Fats - Hetenyi

	Usual Diet		Diet Planned to Insure Undernutrition	
	Range mg. per 100 cc	Average mg. per 100 cc	Range mg. per 100 cc	Average mg. per 100 cc
Obese	544 to 1.117	890	446 to 802	630
Normal	371 to 1.005	591	414 to 997	607

Hetenyi's results could also have well meant that fat which was being mobilized at a normal rate was being oxidized more rapidly. Criticism is that if it were true that adipose tissue cells of obese individuals resist mobilization of fat in undernutrition, then such persons would not lose weight, or if they did, the loss could represent the destruction of body protein.

Studies show that obese persons are less likely to go into negative nitrogen balance when underfed than are normal individuals. Keeton and Bone (35) in 1933 conducted rather extensive experiments on nitrogen excretion in obesity. Their studies were made with obese patients on caloric diets from 40 to 50 per cent below actual requirements and from 30 to 40 per cent below basal requirements. The patients were permitted to be ambulatory. The patients remained in positive

nitrogen balance. The retention of nitrogen was definite with a majority of values between 1 and 2 gm. per day, with some higher values of 2.2 gm., 2.25 gm., and 5.05 gm. Keeton and Dickson's findings indicate that the stored fat is mobile and easily provides a readily accessible supply of energy. The usual sequelae of undernutrition thusly fail to develop, provided that adequate amounts of protein and carbohydrate are supplied for antiketogenesis and for meeting the "wear and tear quota" of nitrogen. The store of fat therefore protects the body against demands for energy.

Strang, McCluggage and Evans (59) found that obese persons receiving only 440 calories and about 1 gm. of protein per kilogram of ideal body weight do not lose body protein despite this severe undernutrition.

Block (9) felt that further investigation in this field with similar nitrogen balance studies would be of greater aid in determining the validity of this theory. He made studies over a comparatively long period of time in conjunction with the determination of total blood lipids. He had 3 obese women and 3 normal women for control placed on constant daily diets of known nitrogen content. Total daily protein intake was always higher than one gram per kilogram of ideal body

weight. The initial caloric value of the diet was approximately 80 per cent of the basal requirement of the individual. This was decreased 20 per cent at weekly intervals until by the fourth week the caloric value of the diet was only 20 per cent of the basal requirement. Table 1. shows the data for the obese subjects. In each instance, with one exception, positive nitrogen balance was maintained throughout the entire experiment. Blood lipids varied considerably with some tendency to rise during the early days of undernutrition, but to fall later to nearly their initial values. Table II. shows the data for the control subjects. Some tendency was shown for a negative nitrogen balance to occur but the blood lipids varied essentially in the same direction as for the obese subjects.

(see next page)

Table 1. Block, M.

Nitrogen balance, Total Serum Lipids, and Weight Loss of Obese Subjects during Undernutrition.

Subject	Diet	Days	Nitrogen Balance	Total Serum Lipids Mg.%	Average 24 hour Heat Product.	Weight Loss (lbs) Actual	Weight Loss (lbs) Predicted
B.B.	Ad lib.			699.9			
Ht. 5'6½	80 % basal	7	+1.61	807.7			
Wt. 281	60 % "	7	+0.87	868.1	2932	19.75	19.6
	40 % "	7	+0.40	910.0			
	20 % "	11	-0.37	710.0			
	20 % "	7	-0.37	493.0			
L.W.	80 % "	7	+1.21	574.4			
Ht. 5'7¼	60 % "	7	+4.62	700.0			
Wt. 248	40 % "	7	+3.59	850.0	2409	17.0	17.1
	20 % "	7	+1.20	950.0			
	20 % "	7	+1.20	630.0			
O.P.	80 % "	7	+1.09	700.0			
Ht. 5'7	60 % "	7	+1.69	856.0	3000	11.0	10.5
Wt. 227	40 % "	7	+1.60	610.0			
	20 % "	7	+1.70	605.0			

Results produce no evidence of obese subjects oxidizing their body protein leaving the conclusion that they were utilizing their own body fat. The latter appears to be as easily available for heat production as in normal individuals. Results also fail to produce confirmation of Hetenyi's contention that there is a difference in response of the total derum lipids in obese and in normal subjects to underfeeding.

These studies show that obese persons release fat from the stores as a source of energy as readily as normal persons. In fact, perhaps more readily, since

they remain in nitrogen balance when underfed in contrast to persons of normal weight not doing so.

Table II. Block, M.

Controls.

Subject	Diet	Nitrogen Balance	Total Serum Lipids Mg.%
Ht. 5'5"	Ad lib.		
Wt. 124.5	80 basal	- 1.12	523
	60 "	- 0.08	706
	40 "	- 1.40	846
			703
Ht. 5'4"	80 "	+ 1.63	610
Wt. 122.5	60 "	+ 0.76	750
	40 "	+ 0.26	843
			607
Ht. 5'3"	80 "	+ 0.21	499
Wt. 113	60 "	+ 2.21	710
	40 "	+ 0.82	806
			542

WATER METABOLISM

For a good many years it has been known that with changes in diets variations in weight occur. These are due to some extent to the retention or loss of water loosely bound in the tissues of the body. It is well known that an individual may maintain perfect health and keep the water content of his body at an adequate level for all his needs, whether he takes two pints or twelve pints of water daily. The intake of water appears to be regulated almost entirely by the central nervous system. This is largely by the more developed parts of the system which are concerned with the appetite or thirst. The process of regulation, in the normal individual, aside from appetite and thirst appears to be carried out at the opposite end of the cycle; namely, by the kidneys and skin. A more than adequate reserve store of water is held in the body. This is a phenomenon demonstrated in states of emergency when sudden and prolonged deprivations of water are brought about.

Grafe noted the tendency of obese patients toward water retention. Bauer frequently mentioned the association of obesity and disturbance of the water and salt balance. He (3) believed that many persons have a hydrophilia of the tissues, and that it was even possible

to take water out of the air. He conducted an experiment wherein the subject, without having ingested any food, increased his weight by several hundred grams. He believed this abnormal tendency for storing fat exhibited by the subcutaneous cellular tissue varied greatly in different parts of the body and was subject to nervous and endocrine regulation. He felt this tendency was of the nature of a constitutional predisposition and inherited nearly always in the dominant form.

Gamble and Tisdale (22) illustrate the appreciable body water loss which can occur. Their research in determining the amount of water lost during fasting employed calculations in terms of fixed bases. They were thus able to determine the amount of cellular storage. On the basis of their computations the loss of water during the 15 day fast of one of their subjects amounted to 62 per cent of the loss of body weight.

Intracellular water lost

1. Due to destruction of protoplasm---1,620 cc
2. Due to reduction of cell volume---- 420

2,040 cc

Extra-cellular water lost---------- 320

Total loss of body water----------2,410

Loss of body weight----------3,920

Body weight loss due to water------ 62 per cent

They held that the body water lost was due to the destruction of protoplasm with release of its water content and a reduction of tissue glycogen causing a decrease in cell volume.

Bartels and Blum (2) became interested in this subject upon noticing a disturbance in water balance while engaged in a routine examination of one of their patients. They then made determinations on members of the nursing staff of two large hospitals. They included in their studies, obese persons as well as normal control subjects. The test consisted of giving 1,500 cc of water and collecting the urine at hourly intervals thereafter. The percentage over and under weight was calculated and routine urinalyses were performed. Their results do not indicate that obese subjects retain fluids to a great degree, for in only 7 per cent was the output less than 1000 cc. The retention of water was more marked in underweight subjects. By using the Volhard dilution test, they did find, however, that obese subjects not on a diet did show slight retention of water.

Per cent of subjects in each group with output of more than 1500 cc and less than 1100 cc of urine.

More than 1500 cc	Per cent
0 - 10 per cent underweight	33
0 - 10 per cent overweight	40
More than 10 per cent underweight	28
More than 10 per cent overweight	34

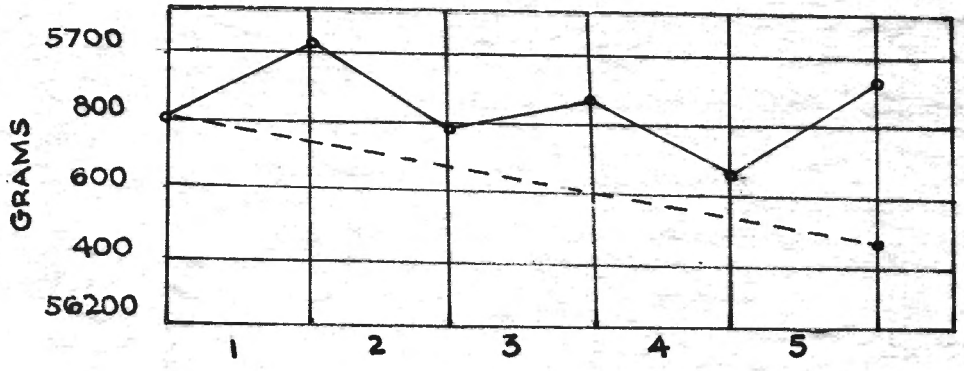
Less than 1000 cc	Per cent
0 - 10 per cent underweight	23
0 - 10 per cent overweight	7
More than 10 per cent underweight	28
More than 10 per cent overweight	28

Newburg and Lashmet (45) provide evidence supporting the theory of water retention. The following figures illustrate some of their results:

(see next page)

Paradoxical gain of weight by normal subject.

	Proteins	Fat	Carbohyrates	Calories
Metabolism	69	86	148	1688
Diet	63	26	148	1078
Body losses: Solids	6	60		
Preformed water	18	6	= 90 gm. daily	
Total	24	66		



Actual gain = 115 gms.
Tissue loss = 450 gms.

Fig. 2. A normal man may gain weight while being underfed.

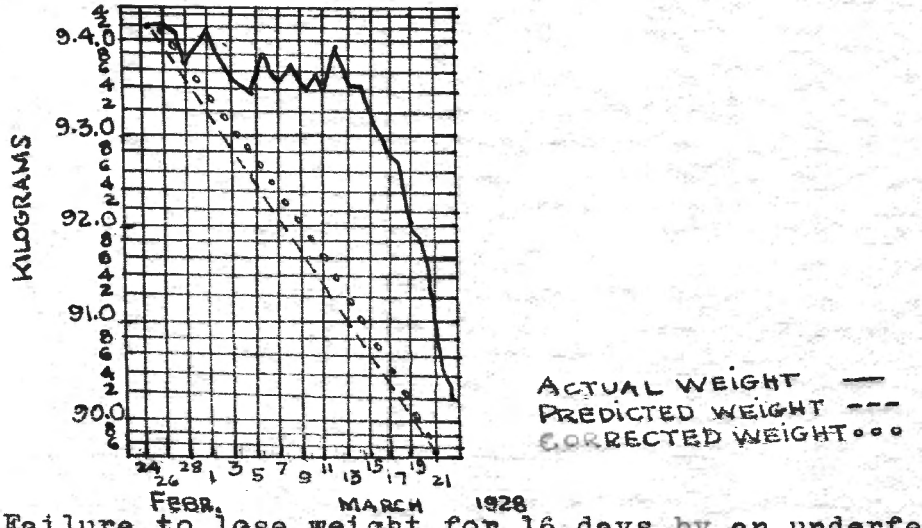


Fig. 3. Failure to lose weight for 16 days by an underfed, obese subject is entirely explained by retention of water.

They feel, however, that since this phenomenon may be regularly produced in the normal subject, attempts to attribute it to inherent abnormalities of metabolism in the case of obese are unnecessary. As the result of all their studies, they concluded that all obesity comes under the heading of simple obesity.

Strang and Evans believe that in obese persons the normal storage capacity of water is greatly increased due to the great capacity of fat tissue for water storage. During periods of rapid fat tissue loss the spontaneous alteration in this storage capacity that normally occur are exaggerated to a greater magnitude. It was their feeling that Newburgh also proved this.

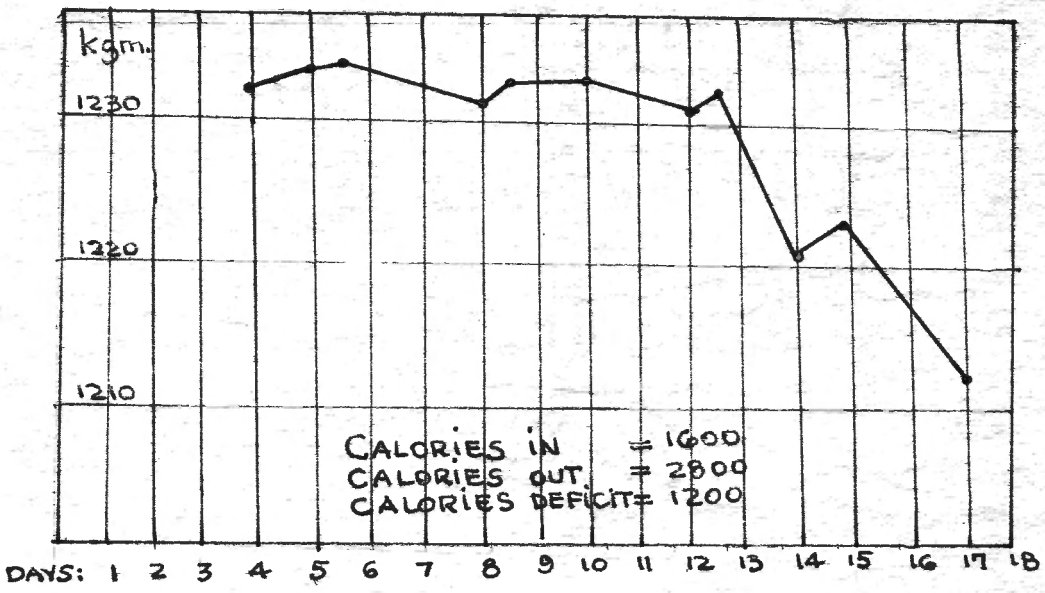
Wohl stressed the importance of water storage as a possible factor in the etiology of obesity. He reported satisfactory results from the intravenous use of salyrgan in a group of patients who failed to lose weight on a strict sub-maintenance diet. The stationary level of weight was attributed to hidden water retention.

Hoffman (32) also believes that obesity may often be the result of accumulation of fluid in the fatty tissues. He states that the water is often difficult to eliminate and requires the use of diuretics to force it out.

Perhaps one of the most widely recognized studies regarding water balance is that of Newburgh and Johnston (72). Their experiments were elaborate and painstakingly carried out in determining the water balance of a series of fat persons during periods of underfeeding. An idea of the extensiveness of the experiments may be gained from the following: (1) the water drunk as such; (2) the water content of the blood; (3) the water made by oxidizing the hydrogen of the metabolic mixture; the preformed water which is held by the body tissues and released when they are destroyed to supply energy.

Consideration was therefore made for the total water intake. They considered the water that left the body as the sum of the (1) water of the urine; (2) water of the stool; (3) water lost insensibly from lungs and skin. Their experiments considered obese as well as non-obese subjects. They refute the belief by many that some persons are endowed with a special type of metabolism which, seemingly, is not regulated by the law of conservation of energy. They feel that if the conditions which caused a plateau in the weight curve be continued for a few more days it will be observed to make an abrupt downward inclination in the curve. They

feel that the individual is now losing weight at a much more rapid rate than can be accounted for by destruction of body tissue. This excessive loss of weight continues until the total loss calculated from the beginning of the plateau approximately equals the predicted loss due to oxidation of body tissue.



Calories in = 1600
Calories out = 2800
Calories deficit = 1200

Fig. 4 Undernutrition, a plateau in the weight curve is followed by an excessive loss of weight.

ENDOGENOUS OBESITY

Contrary to earlier teachings, endocrine obesity appears to be relatively rare. A diagnosis of endocrine disturbances on the basis of adiposity is not uncommon, but support of such diagnosis with strict scientific data is lacking.

The diagnosis of pluriglandular disease is often made simply because of excess fat deposition about the hips and trunk, especially when associated with menstrual disorders. It is perhaps often overlooked that the hips and trunk are the most common sites of fat accumulation in normal persons on an excessive diet. In this respect it should be remembered that obesity in itself can induce ovarian disfunction and that these conditions disappear spontaneously following weight reduction.

Chief points of disagreement exist regarding which gland or group of glands are responsible, the age of incidence, site of disturbance, etc; but it is conceded by the majority of investigators that a relatively small percentage of the cases can be explained by an endocrine abnormality. Some investigators have made observations and interpretations favoring the endocrine concept. These include such observations as hereditary tendency, suddenness of weight onset, characteristic distribution,

failure to lose weight upon attempted dieting, and frequent history of obese patients who profess to be small eaters. Interpretations are so variant, however, that these may be taken to have just the opposite significance.

Bauer believes that though endocrine dysfunction may be a cause of obesity, these cases form an insignificant portion of the obese patients that present themselves at the clinic. He cites the dangers of an "endocrine diagnosis" in cases which, upon more careful study, might reveal a more likely basis for obesity. Bauer (3) in an earlier study found that only 2.6 per cent of 275 cases of obesity had their origin in clinically detectable disturbances of the glands of internal secretion.

Kupp (38) in attempting to make studies of the anatomical and histological aspect of obesity reported on 31 autopsy findings of unselected obese individuals. In 5 of the cases all endocrine glands were found to be intact. In 26 cases some pathologyof one or more glands was demonstrable. Most common demonstrable lesions were those of the 14 cases involving the pancreas. These consisted in lipomatosis with atrophy of the parenchyma or obstruction of the pancreatic duct due to gall stone disease or inflammation. The Langerhans "islets" appeared to be hypertrophied in most cases. Other cases showed

fibrosis and lymphocytic infiltration of the hypophysis (2 cases), hypertrophy of the pineal gland (2 cases), adenoma in the adrenal cortex (2 cases), pluriglandular changes consisting in hypertrophy and adenoma of the pancreatic islets, enlarged hypophysis with cysts in the anterior lobe and pars intermedia, and involution of the thyroid, (1 case).

Zeynek's material comprised 32 cases of "constitutional obesity". The most common finding was an increased number of the basophilic cells in the anterior lobe of the hypophysis. There was a relative increase in the number of cells in 72 per cent of the cases, absolute increase in 81 per cent, "marked" increase in 17 cases, "very marked" in 9 cases, and no case showed a decreased number. The highest number of basophilic cells were found in extremely obese persons. Histological examination of the pancreas in 17 cases showed more or less lipomatosis and atrophy. The remainder of the endocrine glands, such as the thyroid, adrenals, ovaries, and testicles all showed some degree of atrophy.

The results of these findings may prove to be very significant, but it remains to be further investigated and proven before adequate judgement can be passed.

Goldzieher (24) believes much confusion has arisen

from the widely held, though erroneous belief that a low metabolic rate is synonomous with hypothyroidism.

It is not only the thyroid gland which maintains the basal metabolism at a physiological level. The pituitary is also a factor which may stimulate the oxygen consumption even in the absence of the thyroid gland. In addition, the pituitary governs the thyroid. Goldzieher believes that the greatest causal role of the endocrine glands is played by the pituitary, though hypothyroidism, adrenal insufficiency, and the gonads could play a part in the pathogenesis of obesity. He pointed out that in connection with obesity of the so-called pituitary type, retention of salt and water associated with an excessive appetite (possibly caused by hypoglycemia) may add to the excessive weight.

Greene (25) made a study of 350 cases for evidence of increased food intake or diminished activity during the time of gain in body weight. He wished to find evidence of ovarian dysfunction and ability of these patients to lose body weight on low caloric diets. Several of the interesting charts are listed here.

(see next page)

Menstrual History and Relation of Menopause and Puberty to Onset of Obesity	Number	Number of Patients Who Lost Weight on Low Caloric Diets
Normal	126	60
Irregular	34	20
Nearing menopause	4	2
Dysmenorrhea	7	2
Menorrhagia	7	4
Scanty	5	4
Amenorrhea	13	6
Menopause	74	10
Obesity began after	15	6
Obesity began before	50	3
Menses were normal	48	3
Menses were abnormal	2	0
Artifical because of fibroids	4	1
Puberty		
Obesity began before	22	16
Menses normal	17	12
Menses abnormal	5	4
Obesity began with	1	1
Menses irregular	1	1

The incidence of, and types of, menstrual disorders, and the relation of onset of obesity to menopause and puberty are shown in the table. The number of these patients with various menstrual disorders who lost body weight when low caloric diets were followed is also shown. (Greene, Ann. Int. Med. 12.2:1799, 1939)

	Myx-edema	Pituitary Tumor	Chronic Encephalitis	Supra-sellar Tumor	Diabetes Insipidus
Nutritional status					
Obese	6	7	16	1	1
Thin	1	4	19	2	1
Normal	11	7	52	2	5
Relation of obesity to the onset of					
Antedated	4	5	16	1	1
Postdated	3	3	5	0	0
Disappeared with	1	1	5	0	0
Changes in weight after onset of					
Gained	6	5	6	1	0
Lost	5	7	33	2	1
No Change	8	6	16	2	6

Shows the nutritional status of the patients at the time of examination, the relation of the obesity and the changes of body weight to the onset of the other maladies. (Greene, Ann. Int. Med. 12.2:1799, 1939)

Obesity Began in Association with	Number Who Lost Weight on Low Caloric Diets
Pregnancies	22
Illness	23
Impaired locomotion	15
Operations	10
Increase of food intake	2
Chronic encephalitis	3
Myxedema	1
Hypophyseal tumor	1
Insufficient data or negative history	69

Shows that obese patients who will follow low caloric diets for an adequate time will lose body weight regardless of the coexisting disease or the circumstances associated with the onset of the obesity. (Greene, Ann. Int. Med. 12.2:1800, 1939)

67.5 per cent of patients who gave a history of diminished activity while they were gaining weight indicates that many cases of "endogenous" obesity would be eliminated by a more detailed history. A history of increased food intake, however, was present in only 3.2 per cent. Ovarian dysfunction as manifested by abnormal menses or menopause was present in about 50.6 per cent.

Rony (52) made a very extensive study of his own series of 250 obese adult patients in addition to juvenile. He made a search for endocrine disturbances, basing his diagnosis upon the following: history and on observations pertaining to the growth and sexual and mental development of the patient and family, all in addition to laboratory procedures, such as determination of basal metabolism, dextrose tolerance tests and roentgenographic study of the sella turcica and bones of the hand. Only six of these were found to be entirely free from glandular disturbance as judged by these examinations employed. This group of obese adults included 192 women and 8 men, average age 31 years, average excess weight 66 per cent. Definite endocrine syndromes were found in only 13 cases and a diagnosis of possible endocrine disturbance in 56 cases. In many of these the exact localization of the glandular disturbance could not be determined. Of the

adult patients, 131 were apparently free from endocrine disturbance. In the majority of cases various combinations of abnormalities were present and included accelerated or delayed somatic development, sexual infantilism, high or low sugar tolerance, extremely small or large sella. The abnormalities were interpreted as being due to glandular disturbance in at least 34 cases or 68 per cent. 15 of these cases were classified as various forms of pituitary, one as hypothyroidism, 18 as either pituitary disturbance or primary hypogonadism.

In his work he separated the findings from the 50 juvenile and 200 adult obese patients. The juvenile age represents a sensitive test period for the clinical detection of glandular disturbances in view of the marked effects of the glands on somatic, sexual, and mental development. Therefore, endocrine disturbance in children is more easily detected. Accordingly, the actual incidence of the disease might be quite different in obese children and obese adults.

In interpreting the coincidence of endocrine disorders and obesity some of the following relations may be considered:

1. High incidence of glandular disturbances in obese patients.

2. Glandular disturbance might be a sequel of obesity.

3. Topographical relationship of the structures involved. These may involve embryological, anatomical, and functional relations.

4. Coincidence may be due to hereditary linkage of genes.

5. Hormonal substances from the glandular disturbances may determine the deposition of fat.

The majority of authors conclude that none of these theories may be applied to all or even a large percentage of obese patients. Whatever the etiologic factor is, the greatest number of these patients will respond to a restricted diet without the use of endocrine preparations or roentgen therapy.

THYROID

The thyroid gland is one of the endocrine organs perhaps most frequently associated with obesity. The association of a hypothyroidism with a frequent cause for obesity is usually based upon a diagnosis of a basal metabolic rate between a -10 and +25 per cent--with or without the clinical symptoms.

Goldzieher (24) feels that a too extensive as well as erroneous belief has arisen from associating a low metabolic rate necessarily with hypothyroidism. He believes that the thyroid is only one of the many factors which maintains the basal metabolism at a physiological level. The theory exists that with an appreciable drop in basal metabolism a corresponding decrease in oxygen consumption in the resting state occurs. This is supposed to indicate an abnormal economy of the ingested food and therefore account for a tendency towards weight increase.

Newburgh suggests more critical analysis before interpreting a low basal metabolic rate as a pathognomonic sign of hypothyroidism. He cites some factors, such as calculations, physical and psychic attitudes, etc. as important affectors of the true test results.

Newburgh, disturbed by this perplexity regarding the true evaluations of basal metabolic rates, consulted with Means, who for many years directed the thyroid clinic at Massachusetts General Hospital.

Means (44) believes that for a better analysis of the functional activity of the thyroid gland, blood levels of the iodine, as well as basal metabolic rates, should be observed.

However customary it is to associate obesity with an insufficiency or lack of thyroid hormone, extensive clinical material shows convincingly that this is not a common cause of obesity. These findings persist despite the fact that thyroid medication, by virtue of its character as a metabolic stimulant, is used effectively even in cases in which obesity developed on different grounds.

Warfield (65) observed in 88 cases of hypothyroidism that 24 per cent had gained weight, 25 per cent had lost weight, and 51 per cent experienced no weight change.

In Rony's series of 250 consecutive cases of obesity (52) he found conclusive signs of hypothyroidism only in 1 juvenile and 3 adult patients.

PITUITARY

The importance of the pituitary in the pathogenesis of obesity has come more and more to the forefront in recent years.

Hetherington (31) injected chronic hypophyses of rats in the attempt to check any possibility of some sort of selective deterioration of the hypophysis which might be responsible for some pathologic obesity. Few animals evidenced any perceptible degree of fat deposition, but necropsy on those animals which did evidence overweight revealed considerable hypothalmic damage in addition to destruction of the hypophysis. In subsequent experiments in which hypothalmic lesions were made without involving the hypophysis, almost 100% of the animals became obese.

Hetherington concluded that perhaps obese lesions in the hypothalmus or in a hypophysial-hypothalmic pathway may be of importance in the pathogenesis of obesity.

Patients with enormous obesity are characterized by shoulder and pelvic girdle adiposity. They have large busts and hips, small facial features, hands, feet and tapering fingers. The pituitary has been connected with such syndromes as adiposogenital dystrophy or obesity of the "girdle" type. This has been known for a long time,

but erroneously ascribed to lesions of the posterior lobe or hypothalmus; yet, according to recent work, the role of the anterior lobe seems to be more significant. This is borne out by the demonstration of direct calorigenic hormones in the anterior lobe beside the trophic influence upon the thyroid, and by the secretion of a fat metabolism or ketogenic hormone.

Pituitary obesity may start in childhood as part of the Froehlich's Syndrome. Froehlich described and studied such a case in detail. He attributed this syndrome to a disturbance of the hypophysis. A usual accompaniment is delayed sexual development with some retarded general growth. This condition differs from hypothyroidism by its distribution previously mentioned but largely by its lack of inactivity even stupidity, though the sexual development is usually retarded.

Since then Rony cited a number of cases of similar conditions proved at autopsy, but he also pointed out that poor nutrition was not uncommon in other cases of proved hypophysial tumor. Criticism regarding his initial discovery and publicity of this case is that there is nothing in his original report to indicate that obesity was anything more than incidental. The author further mentioned that even emaciation was commonly

encountered in cases of hypophysial tumor. Froehlich's fame as a neurologic surgeon appeared to lend a biasing acceptance of his findings.

Subsequent experimentors attempted surgical injury to the hypophysis and hypothalmus with an effort of determining their relation to the development of obesity. Due to the close anatomical relationship of these two structures it became a matter of conjecture as to which of the two were the prime instigators of obese pathology.

Smith (14) finally was able to demonstrate rather satisfactorily in the rat, hypophysectomy without injury to the hypothalmus. In this experiment he obtained complete arrest of growth, cachexia, loss of weight, and atrophy of the thyroid, adrenal cortex, and gonads. Since then experimental demonstration has successfully proven this relationship. Though a total hypophysectomy in the rat demonstrates a subsequent loss in weight, the possibility remains that perhaps a partial hypophysectomy may cause an obese state.

Cushings syndrome or basophilic adenoma is another form of pituitary obesity. It occurs in relatively young adults with rapid onset. Its distribution is confined to areas about the face, neck, thorax and abdomen. The obesity is of the upper body or "buffalo" type.

There is amenorrhea in the female, regression of genitals and impotency in the male. In addition there may be hirsutism in women, hypertension and certain roentgen ray and laboratory findings.

Water retention is another type of obesity which may be classified as being due to a pituitary disorder. This is thought to be the result of the hyperactivity of the water hormone, an essential hormone of the posterior lobe. These patients give a history of rapid weight gain and present characteristics of a pituitary adiposity. These cases are found to be resistant to the usual therapy for obesity and require a more drastic measure, such as diuretics. This condition may be just the opposite to that of diabetes insipidus in that the latter is the result of a deficiency of this hormone.

PANCREATIC OBESITY

Noorden in 1900 was probably the first to suggest that the pancreas may be responsible as a pathogenic factor in obesity. Falta later appeared to support Noorden's view.

In considering the factors which influence storage of fat one must consider the possible effects of hyper-insulinism. It is well known that clinical diabetes is frequently preceded by a gain in weight. Blotner (74) Metz (75) and others reported good results in using insulin in the treatment of lean individuals. This observation led to the belief that obese individuals might be in a state of hyper-insulinism, as the result of hyperactivity of the pancreatic islets.

Most observers agree that many patients with hyper-insulinism are frequently obese. Fancher (20) believes that an excess of pancreatic secretion may ultimately be found to be the underlying cause for all obesity.

Patients with pancreatic island tumors may demonstrate an initially great accumulation of fat. Insulin when used in lean subjects is known to cause a gain in weight. Experimentally it has been observed that the injection of insulin into animals or persons receiving food rich in carbohydrate, may result in respiratory

quotients frequently exceeding unity, indicating a possible conversion of carbohydrate into fat.

Rony (52) found the incidence of hyper-insulinism in his series of 166 unselected cases of obesity was very low. Less than 70 mg. per cent fasting blood sugar was found in 9. The lowest value was 62 mg. per cent. Only one case was classified as a mild hyper-insulinism.

Harris reports that a history of over-indulgence in sweets is frequent in patients with hyper-insulinism. The observation that craving for sweets is frequently present in obese subjects without an accompanying hypoglycemia or clinical symptoms indicates that their craving for sweets is not due to hyper-insulinism. One could therefore conclude that hyper-insulinism in itself does not cause obesity, even when present.

GONADAL OBESITY

It has long been recognized that castration is a cause of adiposity. This principle has been utilized by breeders of domestic animals for fattening. This effect is strikingly shown in the domestic fowl. An increase of 25 per cent has been noted in a fully grown capon. Similar effects are well typically illustrated in castrated adults of harems. Later observations of such conditions as eunuchoidism, secondary hypogonadism, pregnancy and menopause resulted in an association of these conditions with anomalies of fat deposition.

Distribution of the fat is rather general with more marked deposits in the general lower abdominal region, hips, and breasts.

Glaevecke (73) followed up the body weight of 40 women who had been castrated at twenty-one to forty-five years of age. Five years after the operation more than 10 lbs. increase in weight was found in 57.5 per cent of the cases. 5 to 10 lbs. increase in 35 per cent and less than 5 lbs. in 7.5 per cent was also noted. This same investigator cites for comparison, changes in weight occuring in another group of women after hysterectomy with the ovaries left in situ. The results were correspondingly 33, 42, and 25 per cent.

Wagner reported observations on 500 actinocastrate women. Within one year 200 had gained more than 5 kg., and 150 showed no change in weight.

ADRENAL OBESITY

Of all the endocrine organs the adrenals are given credit with causing the least number of cases of obesity. These organs when associated with malignancies or hyperplasia of the cortex may produce an obesity similar to that found in the Cushings syndrome or basophilia. The mechanism whereby obesity is brought about here is unknown, but it is definitely known that surgical removal of an infected adrenal organ has been followed by a rapid loss of excess weight.

The adiposity in this condition is not marked. Its distribution is prominent about the girdle region, developing rapidly so as to stretch the skin to form striae and become quite painful. Other symptoms, such as gonadal disorders, hypertension, polycythemia and osteoporosis may aid in the diagnosis.

Patients with Addison's disease, due to destruction of the adrenals, usually become emaciated. Adrenal cortex extracts often bring about an improvement of appetite and weight gain and perhaps this hormone may be tied up with appetite and intestinal resorption of glucose and fat, thought to occur in adrenal deficiency.

EXOGENOUS OBESITY

Exogenous or simple obesity is that type which is attributed to a greater energy intake than an energy output.

The distribution of this type of obesity is usually symmetrical, and is located chiefly under the skin, in the omentum, the mesentery, retroperitoneum, and if extreme, may infiltrate all organs of the body.

Most fat patients like to ascribe their condition to hereditary, or some peculiar quirk in their body chemistry, or to a mysterious abnormality of their endocrine system. After an examination of the scientific literature one is left with the conclusion that the overwhelming majority of cases are the result of faulty habits of eating. These individuals appear simply to eat more food than the body can expend in the form of energy. The residual food is thus stored and is added to the body mass.

Few people admit that they eat more. They are usually self conscious of these larger amounts and though they evidence little eating at regular meal times, they may be constantly indulging in nibbling in between meal times with a resultant greater calory intake. Their estimate of their own intake is notoriously highly

unreliable. Usually an excessively large and poorly balanced diet with a predominance of starchy carbohydrates or fat is invariably found by careful checking.

Preble (50) states that he has yet to see any successful "system" of reducing weight advocated by the profession or advertised by laymen that does not include regulation of the diet. He believes that success in reducing weight is obtained in 100 per cent of the cases that cooperate with the physician.

Hochman showed that in 400 consecutive cases endocrine or other disturbances have been rarely present. He feels that most cases resolve down to the fact that there is a greater intake of food than energy output.

Bauer (4) found that only 2.6 per cent of 275 cases of obesity had their origin in clinically detectable disturbances due to abnormalities or disturbances of the glands of internal secretion.

Greene (25) in his study of 350 cases found a high percentage of patients who gave a history of diminished activity while they were gaining weight. He felt that many cases of "endogenous" obesity would be eliminated by a more detailed history.

HEREDITY

Heredity has long been recognized by many workers to be associated with obesity. Its greater frequency in some families has even been noticed among the laity to be more than a coincidence. The statistics of Bouchard (1882, 14) and Van Noorden (1907, 70) revealed 50 to 60 per cent of patients with "constitutional" obesity having obese parents.

Rony found in his 250 unselected cases of obesity 69 per cent had at least one obese parent, while in 24 per cent both parents were obese. The environmental factor, of course, must be ruled out here for it is common knowledge that some family living and eating habits are very conducive towards occurrence of obesity.

Silver and Bauer (56) demonstrated 88 per cent familial incidence in obesity. They believed that a key to the understanding of obesity lies in a study of the family and an appreciation of the constitutional, familial nature of this process. They cite an example of one of their obese patients. A sister of the patient weighed 83 kg., with a rather notable degree of shortness. Her sister had a daughter who weighed 80 kg. at 17 years of age. They believe that this occurrence of obesity in sister and niece is more than coincidental

and illustrates rather typically their contention.

Fellows (21) made a study of the overweight employees of the Metropolitan Life Insurance Company. Studies of the parents of these overweight subjects revealed an incidence of overweight ten times greater than that of the general adult population. Both parents were overweight in 24 per cent of the cases.

Christiansen (15) illustrates the familial aspect of obesity in infants who gained weight enormously and died of an excessive obesity during the first year of life.

Danforth (17) made an extensive study of the heredity factor in yellow mice. Yellow mice were mated to females of various colors. Some of the descendants were yellow, others were not. Litter mates were kept in the same cage and had access to the same food. Yellow offspring and litter mates of other colors were kept in the same cage and were supplied with the same food in abundance. Only after sexual maturity was attained was there a difference in weight gain. A progressive increase in weight gain was experienced by the yellow mice and particularly so of the females. Since these offspring were all raised in the same environment it is believed that a true hereditary character is demonstrated here. Newburgh (46) believes as

a result of his preliminary studies of hereditary obesity in yellow mice, that mice which become obese eat more than others. He felt that a hereditary bulimia may be evidenced here.

In man, identical twins provide advantageous material for the study of obesity because of their accepted equal genetic endowment and dissimilarities due to their environment.

Wilder (67) believes that heredity is responsible for an abnormal irritation in centers of the diencephalon where feelings of hunger and satiety originate.

It has been noted, not uncommonly, that a marked gain in weight is experienced following encephalitis or a tumor in this region. This phenomenon has also been demonstrated by experimental lesions but a variability in response was noted.

Gurney (26) demonstrated some support to this supposition. He made a study of 63 obese women. He selected these personally and compared them with another group of women of approximately the same age periods who had been subjected to about the same physical and physiological experiences. A difference was noted on the time of onset of obesity. Pregnancy or a major operative procedure appeared to be the commonest factor associated with the onset of obesity in the group of obese women.

Similar results were not noted in the control group. Incidence of obesity in the parents of the stout women, however, was markedly increased above those parents of the controls. Children of these two groups revealed interesting results. 73% of the 89 offspring from matings of stout persons were stout, whereas only 9% of the 176 offspring of the matings of non-stout persons were stout. 41% of the offspring of a stout and non-stout person were stout. He suggests the hereditary factor may help to explain the apparent inconsistency of build in persons subject to the same environmental influences.

Joslin attributes this frequency of stout children with stout parents to habits of overeating acquired from parents, also stout persons appreciate food better and therefore children are more exposed to better food.

Davenport (18) obtained results which seem to indicate that body build follows the Mendelian laws of inheritance. He studied the offspring of parents of similar and dissimilar builds. He concluded that there are 3 gametic factors, one which may correspond to dystrophy of the thyroid, one to dystrophy of the pituitary, and the third may be a metabolic factor affecting the actual metabolism of the cells. Perhaps if this

hereditary factor be accepted, the onset of obesity in one person, as opposed to that in another who is subject to the same environmental influences and diet, may be more readily understood.

Verschuer (62) studied 57 pairs of identical twins varying in ages from 3 to 51 years. He and Newman (47) and his associates made extensive studies with the resultant findings of a definitely greater weight variation than any of the other anthropologic weight measurements. These results emphasize the environmental factor of weight. Verschuer further compared the variations among identical twins living under similar conditions with those in a dissimilar environment. He found variability greater in dissimilar than in identical environments.

Several investigators stress the fact that the great problem of inheritance in obesity is to determine which tissue or organ anlages carry the genetic factors that tend to produce the adiposity of the body. Danforth's (17) observations suggest something of this nature. During his routine work on adiposity of yellow mice he noticed that yellow females were less fertile than non-yellow females and more obese than yellow males. He further noticed that non-yellow females with the

ovaries removed developed weight curves similar to those of unoperated yellow females. Danforth interpreted these observations as a possible relationship between the ovaries and the hereditary transmission of the adiposity of yellow mice. He felt that perhaps further careful histological studies of the ovaries, other endocrine glands, and the midbrain of yellow obese mice in comparison with similar organs of non-yellow non-obese litter mates, might prove of further value on this subject.

CONCLUSIONS

Basal Metabolism:

Painstaking investigation of metabolism of obese individuals has failed to reveal findings to warrant an accumulation of fat. Observations indicate that it falls within normal limits. In fact, a greater heat production is produced by obese individuals than a normal person of the corresponding age, height, and sex, with similar circumstances.

Specific Dynamic Action:

Results obtained by later investigators have failed to find the specific dynamic action reduced or that absorption and metabolization of food occurs with less expenditure of energy.

Luxusconsumption:

Supportive evidence for this theory is lacking.

Lipophilia:

Studies show that the adipose tissue cells of obese individuals release fat from depots as a source of energy as readily as do those of normal individuals. Some exceptions appear to occur in localized areas of fat accumulation, and perhaps heredity may play a part here.

Water Retention:

Conclusive evidence regarding this theory is lacking.

Increased Absorption of Food:

No supportive evidence has been found.

Heredity:

Opinion appears to be divided regarding this. There are those who advance the Mendelian influence as opposed to those stressing the environmental side. Most observers do concede that body types are inherited. Though the mechanism is uncertain, the impression is gained that heredity does play a role in the etiology of obesity.

Cerebral Obesity:

It is accepted that injuries to the hypothalmus may result in adiposity, though their occurrence is extremely rare.

Thyroid:

It is conceded that obesity is possible here, but that the frequency is far less than supposed.

Pituitary:

Malignancies of this organ and injuries to the hypothalmus have been associated with obesity, but their alleged frequency is questioned.

Pancreatic:

Supportive evidence for this theory is lacking.

Gonads:

Some evidence exists that ovarian dysfunction is responsible for obesity, but more data is necessary for conclusive proof.

The etiology of any particular case may vary with that particular individual. It is my belief that heredity plays too great a role to be ignored. Most observers concede that the body types are inherited. Perhaps the transmission of Mendelian characteristics is present here, becoming manifest in the presence of some exciting or precipitating cause within the environment. Further investigation is certainly warranted here.

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