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CALORIC UNDERNUTRITION AND STARVATION, WITH NOTES ON PROTEIN DEFICIENCY

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1. INTRODUCTION

Justifiable enthusiasm about discoveries of specific nutrients and their metabolic consequence has distracted attention from the oldest problem in nutrition—simple caloric inadequacy. General undernutrition, with or without major deficiences of individual nutrients, has always been widespread in the world at large; the tragedy of famine periodically emphasizes how slender is the margin of safety. In the United States and Canada food production has been so abundant for many years that the direct impact of famine is unknown; the consequences of food shortages elsewhere, however, increasingly demand attention and effort here. Moreover, the importance of secondary undernutrition in disease is beginning to be realized.

Caloric undernutrition has been generally assumed to involve a parallel protein deficiency in most cases. In Asia, the area of most frequently recurring famine, the diet is low in protein in the best of times. Any food shortage quickly reduces such sources of proteins as are usually available, and subsistence depends almost entirely on rice, tapioca and other foods which contain little protein. In Europe the protein in the typical famine diet is almost all of vegetable origin. In any case, the severely undernourished person is necessarily in a state of negative nitrogen balance so there is at least some of the effect of a protein deficiency. The present discussion includes some remarks on protein deficiency (sections 7, 8 and 9).

Practical questions about general undernutrition raised by World War II clearly revealed the undeveloped state of this area in the science of nutrition. Generalities about metabolic balance, normal weight for height, and optimal food intakes are of small help in evaluating the actual degree of caloric inadequacy, in predicting the consequences of a specific dietary level and in planning and operating programs of relief and rehabilitation. This is a field in which the contribution of animal experimentation is necessarily small; quantitative translation from animal to man is dubious at best and impossible in terms of behavior, intellective functions, work performance and many details which have great medical and social significance. The residue of useful data on man himself is surprisingly meager but has been greatly augmented in the past few years.

2. SOURCE OF INFORMATION

Limitations of animal experiments have been mentioned; besides the interpretive difficulty, the actual evidence from studies on animals is not great. On man there is a plethora of general impressions and observations from famine areas; besides frequent deficiencies in technical measurement, these reports usually provide only a description of the famine victims without information about their prestarvation characteristics or satisfactory details as to the dietary intakes which produced their present condition. The same strictures may be made about the clinical literature on cachexia. From a vast literature, however, many common points emerge; for the most part these can only be incorporated, without specific citation, in the present summary.

Studies on a few fasting persons constitute the classic literature cited under "starvation" in the textbooks. Acute experiments with no food at all are of great interest, but they have only relatively remote bearing on the problems of chronic undernutrition and the real conditions of famine. Another question is whether the professional fasters and fanatics who have been studied are reasonable representatives of the general population.

There have been two major experiments on prolonged undernutrition in man. The Carnegie Institute experiment [1] provided much information from a group of young men who voluntarily submitted to underfeeding for several months; the degree of semistarvation was small, as indicated by weight losses of only the order of 10 per cent. In the Minnesota experiment 32 young men lost an average of 24 per cent of their body weight in six months; the total period of study lasted almost two years.[2]

There are no recent full-dress reviews of undernutrition and starvation, but several older works are still of great value: Porter [3] for a first-hand account, with many autopsies, of famine in India; Lusk [4] for the metabolic problems; Morgulis [5] for a discussion from the point of view of the biologist, and Jackson [6] for an exhaustive treatment of morphologic aspects. Several recent papers provide good general pictures. Leyton [7] reported observations in a prisoner of war camp where there were some elements of scientific control. Data on weight changes and mortality of internees in France are valuable.[8] Summaries of data on occidental persons starved in Japanese camps are available.[9] Useful vital statistics and estimates of dietary intakes in periods of famine are provided for Holland [10] and for Greece.[11] Data from the siege of Leningrad are interesting.[12]

From the Laboratory of Physiological Hygiene, University of Minnesota.

The present review is mainly an abstract of parts of a book, "The Biology of Human Starvation," which will be published by the University of Minnesota Press in 1948. The greatest single source of data is the Minnesota experiment (1944-1946) Both book and experiment are the joint works of Dr. Ancel Keys and Drs. Josef Brozek, Austin Henschel, Olaf Mickelsen and Henry Longstreet Taylor, with assistance on various phases by Miss Angie Mae Sturgeon and Drs. Samuel Wells and Ernst Simonson.

1. Benedict, F. G.; Miles, W. R.; Roth, P., and Smith, H. M.: Human Vitality and Efficiency Under Prolonged Restricted Diet, Publication 280 Carnegie Institution of Washington, 1919.
2. Keys, A.: Human Starvation and Its Consequences, J. Am. Dietet. **22**: 582-587, 1946.
3. Porter, A.: The Diseases of the Madras Famine of 1877-78, Madras, Government Press, 1889.
4. Lusk G.: The Physiological Effects of Undernutrition, Physiol. Rev. **1**: 523-552, 1921. The Elements of the Science of Nutrition, ed. 4, Philadelphia, W. B. Saunders Company, 1928, pp. 75-117.
5. Morgulis, S.: Fasting and Undernutrition, New York, E. P. Dutton & Co., Inc., 1923.
6. Jackson, C. M.: The Effects of Inanition and Malnutrition upon Growth and Structure, Philadelphia, P. Blakiston's Son & Co., 1925.
7. Leyton, G. B.: Effects of Slow Starvation, Lancet, **2**: 73-79, 1946.
8. Zimmer, R.; Weill, J., and Dubois, M.: The Nutritional Situation in the Camps of the Unoccupied Zone of France in 1941 and 1942 and Its Consequences, New England J. Med. **230**: 303-314, 1944.
9. (*a*) Butler, A. M.; Ruffin, J. M.; Sniffen, M. M., and Wickson, M. E.: The Nutritional Status of Civilians Rescued from Japanese Prison Camps, New England J. Med. **233**: 639-652, 1945. (*b*) Morgan, H J.: Wright, I. S., and Van Ravenswaay, A.: Health of Repatriated Prisoners of War from the Far East, J. A. M. A. **130**: 995-999 (April 13) 1946.
10. Dols, M. J. L., and van Arcken, D. J. A. M.: Food Supply and Nutrition in the Netherlands During and Immediately After World War II, Milbank Mem. Fund Quart. **24**: 319-358, 1946.
11. Valaoris, V. G.: Some Effects of Famine on the Population of Greece, Milbank Mem. Fund. Quart. **24**: 215-234, 1946.
12. Brozek, J.; Wells, S., and Keys, A.: Medical Aspects of Semistarvation in Leningrad: Siege 1941-1942, Am. Rev. Soviet Med. **4**: 70-86, 1946.

3. EUROPEAN AND ASIATIC FAMINE

The details of the effects of caloric undernutrition are modified by many factors, including particularly the previous state of nutrition, the character of the inadequate diet and the presence of intercurrent disease. In spite of individual and local variations, certain patterns seem to be characteristic of European countries on the one hand and Southeastern Asia on the other.

In the European countries, especially the northern and central regions, food shortages generally result in a diet dominated by whole or undermilled grains (mainly wheat), potatoes, turnips, cabbages and garden vegetables. The result frequently is a diet which is surprisingly good, qualitatively, and deficiencies in vitamins and minerals may not be prominent. The protein content is not vanishingly small and ordinarily comprises something like 10 per cent of the calories.

The diet in Asiatic famine tends to depend on starchy and fibrous foods, which are often exceedingly poor sources of proteins, vitamins and some minerals. The common frequency of endemic infections and infestations in Asia is exaggerated under famine conditions. The combinations of these debilitating conditions are endless, but those which most frequently modify the picture of simple caloric deficiency are hypoproteinemia, anemia, dysentery and deficiencies of some of the vitamins. Famine in Asia is attended by more severe edema and anemia and more frequent neuropathic conditions than in Europe. The present review cannot treat of these complications; it deals primarily with the simpler European type of undernutrition.

4. THE INCIDENCE OF GENERAL UNDERNUTRITION

A large incidence of general undernutrition seems to be an inevitable companion of national poverty, and this is chronically the state of affairs in most of Asia and large sections of Africa, Southeastern Europe, Central and South America. Until recently general undernutrition was frequently the lot of the underprivileged or economically unfortunate classes everywhere; crop failures or economic depression quickly resulted in semistarvation for the poor. In the United States this situation, never very pronounced, seems to have disappeared. In the great depression beginning in 1929 there was little caloric inadequacy and practically no starvation. In this country severe general undernutrition because of inability to obtain food does not exist except by peculiar accident for isolated persons; there is no reason to believe that this situation will change.

This does not mean that there is no general undernutrition in the United States. There are recluses, invalids, children and aged persons who are unable or unwilling to disclose their want and who may be missed by the proper governmental or charitable organization. Probably far more numerous are the persons who are generally undernourished because of the presence of disease. Anorexia of some degree is undoubtedly far more common than indicated by the rare cases diagnosed as anorexia nervosa or Simmonds' disease (hypopituitary cachexia). Undernutrition is prominent in the majority of patients with advanced neoplasms. Temporary undernutrition results from most severe infectious diseases and from major injuries and surgical operations.

The question of the incidence of caloric undernutrition in the general population has been raised by the results of some surveys of dietary intake. On the basis of one or another caloric yardstick, termed proper, ideal, adequate, recommended, optimal or required, comparisons are made with the estimated actual intake; if the latter value is less than the theoretic standard the case is labeled caloric insufficiency. Thus Wiehl [13] studied the diets of 1,080 aircraft workers and concluded that "the evidence is strong that a considerable number of these men were below a consumption level believed to be adequate." Further, this author commented on dietary surveys in Toronto, Ontario, and Halifax, Nova Scotia, Canada, to conclude that "it is not unusual for wage earners to eat a diet with less energy than is deemed desirable." [14] The absurdity of conclusions derived from this approach is revealed by data on high school pupils.[15] More than half (55.3 per cent) of these pupils were judged to be calorically undernourished, but analysis of the physical examination data shows that of these undernourished children only 11.1 per cent were underweight while 47.7 per cent of them were overweight by 7.5 per cent or more.[16]

5. CALORIC REQUIREMENTS AND RECOMMENDATIONS

The term caloric requirements is widely used, but so far has escaped precise definition, nor will this be attempted here. With any reasonable definition the requirement will be dependent on body size, age, sex, climate, occupation, personal habits, previous state of nutrition and perhaps race.

It is not possible to draw a fine line between caloric adequacy and general undernutrition, least of all by using the caloric intake alone as the criterion. In a given person caloric balance can be maintained over a rather wide range of body weight and caloric intake, and it is not now possible to conclude whether, in the long run, the optimal condition would be toward the upper or lower end of a range amounting to perhaps 10 per cent or more of the average body weight. Changes in body weights are a different matter, and a person not previously obese who loses 10 per cent or more in weight and continues to lose weight is clearly calorically deficient; roughly the same criterion may be applied to the averages for populations.

Various authorities (e.g., the League of Nations and the National Research Council) have made recommendations regarding caloric intake. These are useful in comparing populations and in planning food production; such validity as they have is that of broad averages, and their application to individuals is unwarranted. By and large, the caloric recommendations of the League of Nations and of the National Research Council may be rather higher than optimal. Slight to moderate decreases in per capita consumption below these recommendations in England and Switzerland in World War II and after were associated with evidences of better health. The role of changes in quality of food in these results is obscure, but certainly no adverse effect can be claimed from the caloric reductions. Fleisch [17] concluded that instead of a required average of 2,400 Calories for sedentary adults, the experience of World War II showed an average intake of 2,160 Calories to be sufficient and even beneficial in Switzerland. In the United States careful studies on caloric intake reveal surprisingly low values in some instances where there is no clinical indication of inadequacy.[18]

13. Wiehl, D. G.: Nutritional Status of Aircraft Workers in Southern California: I. Diets of a Group of Aircraft Workers in South California, Milbank Mem. Fund. Quart. **20**: 329-366, 1942.
14. Wiehl,[13] p. 361.
15. Wiehl, D. G.: Medical Evaluation of Nutritional Status: XV. Caloric Intake of High School Students in New York City, Milbank Mem. Fund. Quart. **22**: 5-40, 1944.
16. Keys, A.: The Refinement of Metabolic Calculations for Nutritional Purposes and the Problem of Availability, editorial, J. Nutrition, **29**: 81-84, 1945.
17. Fleisch, A.: Ernahrungsprobleme in Mangelzeiten: Die schweizerische Kriegsernahrung, 1939-1946, Basel, Benno Schwabe & Co., 1947.
18. Winters, J. C., and Leslie, R. E.: A Study of the Diet of Twenty Women in a Moderate-Income Group, J. Nutrition **27**: 185-192, 1944.

6. FASTING AND ACUTE STARVATION

Both fasting (total abstinence from food) and prolonged undernutrition result in many similar effects such as bradycardia, lowered metabolic rate, hypotension and weakness. But there are also obvious important differences; a few of these may be noted simply to emphasize the point that results in fasting experiments cannot be applied in any detail to problems of chronic undernutrition. Prolonged fasting has its intrinsic scientific interest, but it is rarely encountered in nature.

All reports on fasting are in agreement that the sense of hunger quickly disappears as the fast is continued. If the subject is sedentary, hunger is seldom disturbing after the third day and is usually entirely absent in a week. This loss of hunger is much accelerated by physical work. In experiments in the Laboratory of Physiological Hygiene fasting young men doing hard physical work lost the sensation of hunger in twenty-four hours and incipient nausea, with the attendant revulsion to food, was troublesome on the second or third days. This is in sharp contrast with undernutrition in which the sense of hunger progressively increases until it occupies a major part of the consciousness. Only near the termination with death from starvation does the condition change to resemble that in total fasting. Besides such differences in physical sensation, there are decided tendencies to differences in emotional state. Depression and apathy are almost universally observed in persons with severe undernutrition but in sedentary fasting euphoria and states of excitement are not uncommon.

It may be presumed that fasting is a greater, certainly a more abrupt, emergency and therefore a stronger stimulus to mobilize defense mechanisms in the body. This, together with the simple factor of time, may account for some differences in the blood chemistry compared with that in chronic undernutrition. The concentration of both erythrocytes and leukocytes in the blood of fasting persons tends to remain within relatively normal limits, though subject to variations from time to time. Simple undernutrition, however, tends to produce a leukopenia and a progressive anemia.

Perhaps the most striking differences between total and partial inanition are related to the differences in carbohydrate metabolism. Only a small supply of exogenous carbohydrate (which may be supplied also from exogenous protein) suffices to prevent ketosis. The amount required for this—of the order of 600 Calories per day—is usually obtained even in the worst conditions of famine. In any event, ketosis and ketonuria do not ordinarily appear in chronic undernutrition but pronounced ketosis develops in a few days of fasting. Associated with this difference in respect to ketosis are differences in the respiratory quotient, in acid-base balance and in the blood sugar level.

In the studies in the Laboratory of Physiological Hygiene there were observed interesting differences in the relative resistance of various functions to fasting on the one hand and to prolonged undernutrition on the other. For example, strength, as measured in single maximal exertions, is relatively resistant to fasting but is definitely reduced by prolonged underfeeding. In contrast, the coordination of movements is more strikingly reduced by fasting than by semistarvation.

7. PROTEIN DEFICIENCY AND REQUIREMENTS

Pure protein deficiency, with adequate calories and vitamins, is probably seldom encountered in nature, and little is known about it in man. That it retards or reverses growth and leads to hypoproteinemia and anemia is clear. In Asia it contributes to the picture of famine edema and probably frequently complicates the decision as to whether there is a major deficiency of calories or thiamine. Protein deficiency will be considered here mainly as it may be associated with general undernutrition or may be confused with it.

Where caloric inadequacy exists the importance of the protein intake is dubious because the protein tends to be used as fuel in place of fat and carbohydrate and thereby is deprived of its ordinary important function. At exceedingly low levels of caloric intake—below 1,000 Calories daily for an adult—the substitution of protein for carbohydrate in the diet has practically no effect on the balance and the net nitrogen loss from the body continues. At higher but still inadequate levels of caloric intake it may be that dietary protein may spare some nitrogen loss, but the evidence is not fully satisfactory.

As in the case of calories, the concept of protein deficiency also involves consideration of protein requirements; presumably deficiency exists when requirements are not met. The situation is more complicated with proteins than with calories because there are several modifying factors. On the other hand, the criteria for establishing protein requirements are, at first glance, simpler and more objective.

In the growing animal it is customary to consider the least amount of protein which will allow the maximal rate of growth to be the requirement. Clearly this is the requirement for maximal growth, but for what else? Whether this level is optimal is an abstruse question which is seldom asked and which, actually, may be unanswerable without more precise definition. Optimal for what? In the case of animals the only values which are readily examined are size and appearance, physical health—meaning merely the absence of disease and defects—and longevity. The latter is infrequently considered, perhaps because the small evidence available points to an inverse correlation between rate of growth and eventual longevity. Numerous factors of great human value which may be affected by the level of protein nutrition are almost never considered, let alone evaluated.

In the adult the usual criterion for the protein requirement is the least intake level which will maintain nitrogen balance. In practice the method is more troublesome than in theory because of the tendency to spontaneous variation and the difficulty of obtaining exact balance. The expedient of measuring nitrogen excretion in fasting or on a protein-free diet is used to get a minimal estimate of the endogenous protein destruction, but this does not tell how much intake of a particular protein or protein mixture will result in nitrogen balance.

Labile protein reserves (depot nitrogen) in the body are generally considered to be very small, and a sizable negative nitrogen balance for more than a day or two is taken to mean tissue depletion or destruction. But there are situations in which a negative nitrogen balance seems to be physiologic or at least difficult to avoid and perhaps harmless.

8. NITROGEN BALANCE AND PHYSICAL ACTIVITY

Protein catabolism is not increased in muscular exercise; the protein requirement is not altered by participation of protein in the direct energetics of physical activity. This does not mean that the nitrogen balance and requirement are independent of the activity in the long run.

In bed rest, which is the most frequently prescribed therapy in all forms of disease and injury, the nitrogen balance quickly becomes negative on any ordinary diet and this occurs even in the absence of disease or injury; on the resumption of normal activity the nitrogen balance of the patient becomes positive. This phenomenon would seem to be a kind of disuse atrophy; probably most of the nitrogen lost comes from muscle cytoplasm and there may be no actual cellular destruction, at least at first. Similarly, chronic intensification of activity and muscular exercise calls for increased sarcoplasm and therefore nitrogen retention (exercise hypertrophy). It is puzzling, however, to find that even in bed rest and in the presence of situations that involve destruction of tissue there may be a positive nitrogen balance if the protein intake is forced to extremely high levels.[19] Decreases in hemoglobin and plasma protein may occur in infections even when nitrogen retention is good.[19a]

Somewhat similar difficulties arise from the fact that a definitely positive nitrogen balance in adults may be induced by some hormones, notably testosterone propionate. It is difficult to avoid the conclusion that the old discussion of protein reserves must be reopened. Since no specific reservoir of labile protein can be found, it may be suspected that the tissue cells in general have some nitrogen reserve and storage capacity.

In any case, the concept of protein requirements seems less simple and precise than might have been hoped. The optimal protein intake may be something else again, but there is little evidence as to quantitative relationships. The recommendations of many authorities, including the League of Nations and the National Research Council, tend to fix on 1 Gm. of protein per kilogram of body weight for adults. But in studies on young men doing hard work in the open no advantage was found for intakes greater than about two-thirds this amount, even when much of the protein was from vegetable sources.[20] This tends to be in agreement with recent careful studies on nitrogen balance, in which it was concluded that the National Research Council recommendation for a 70 Kg. man could be reduced to 50 Gm. and still provide approximately 30 per cent margin above requirements.[21]

The conclusions indicated in the preceding paragraph will be challenged by those who believe that neither crude nitrogen balance nor performance in normal health tell the whole story. Large excesses of protein intake have been suggested to be advantageous in building up reserves or antibodies, which may be called on to meet the emergencies of disease or injury. The evidence is still controversial except in the case of persons who have been in negative nitrogen balance and in whom a period of positive balance may be restorative. But elevated protein intakes are not clearly detrimental, though they are expensive, and will undoubtedly be recommended by many nutritionists to be "on the safe side."

9. PROTEIN QUALITY

Long ago animal feeding experiments with different individual proteins demonstrated differences in quality; the protein requirement was different for the several proteins. Some of the vegetable proteins were notably inferior to the animal proteins, and it became customary to believe that a considerably greater intake of vegetable proteins was required as compared to animal proteins. Some of this difference could be traced to differences in digestibility and absorption, but more important discrepancies were related to metabolic utilization. It is now agreed that the last is dependent on the amino acid composition of the proteins. Inadequacy of one essential amino acid limits the synthesis of the tissue proteins which must contain it and thereby leaves excesses of the other amino acids which are then useless for this purpose. Accordingly, general protein deficiency may result from lack of a single amino acid.

In actual practice, that is, under the great majority of natural conditions, the importance of protein quality is much less than previously supposed. In ordinary diets, even of the vegetarian type, the protein moiety is made up of many different proteins and the chance that all of them will be low in one or more amino acids is small. On diets of limited variety, however, it is possible to have conditions like the earlier rat experiments in which substantially all the protein is supplied by a very few proteins. Such a condition may easily arise in famine areas; in such cases the provision of small amounts of foods rich in the missing amino acids may be highly beneficial.

An example of unsuspected amino acid deficiency and an interrelationship with a vitamin has recently emerged in pellagra. It now appears that pellagra may result from a deficiency in either tryptophane or nicotinic acid and may be successfully treated by either the amino acid or the vitamin.[22] This means that the protein requirement may be altered by either its tryptophane content or by the amount of nicotinic acid in the diet. It is entirely possible that other similar relationships between amino acids and vitamins will be discovered. The protein requirement is certainly not an independent entity.

10. THE PROBLEM OF BODY WEIGHT AND FAT

Caloric inadequacy produces a weight loss or a low level of weight for height. In practice, dependence in diagnosis is usually on the height-weight relationship; this means comparison with some set of standards. It is essential to recognize the derivation and limitations of such standards. Since there are as yet neither theoretic nor experimental bases for establishing ideal or optimal relationships between height and weight, recourse is had to averages of supposedly healthy groups which are taken as the standards. The body weight of a given person is then compared with the average of a group of healthy persons of the same sex, age and height. The difference between the individual and the group average is then expressed as pounds overweight or underweight. As an added refinement allowance may be made for body build or type, with standards being broken down into groups such as large frame and small frame. There is no agreement as to how these body types may be properly segregated.

Regardless of refinements of measurements and classification, all these standards involve some major uncertainties. First, the designation healthy in the reference group means only the absence of obvious disease and defect, and all persons in the reference group are presumed to be equally healthy, a presumption without basis and certainly false if it is admitted that health has gradations. Second, it is assumed implicitly that

19. (*a*) Spense, H. Y.; Evans, E. I., and Forbes, J. C.: The Influence of Special High Protein Diet on Protein Regeneration in the Surgical Patient, Ann. Surg. **124:** 131-141, 1946. (*b*) Howard, J. E., and others: Studies on Convalescence: Nitrogen and Mineral Balances During Starvation and Graduated Feeding in Healthy Young Males at Bed Rest, Bull. Johns Hopkins Hosp **78:** 282-307, 1946.

20. Darling, R. C.; Johnson, R. E.; Pitts, G. C.; Consolazio, F. C., and Robinson, P. F.: Effects of Variations in Dietary Protein on the Physical Well Being of Men Doing Manual Work, J. Nutrition **28:** 2 3-281, 1944.

21. Hegsted, D. M.; Tsongas, A. G.; Abbott, D. B., and Stare, F. J.: Protein Requirements of Adults, J. Lab. & Clin. Med. **31:** 261-284, 1946.

22. Krehl, W. A.; Teply, L. J., Sarma, P. S., and Elvehjem, C. A.: Growth-Retarding Effect of Corn in Nicotinic Acid-Low Rations and Its Counteraction by Tryptophane, Science **101:** 489-490, 1945. Salmon, W. D.: Relation of Corn Products to the Requirement of the Rat for Dietary Nicotinic Acid, J. Nutrition **33:** 169-175, 1947.

the average somehow connotes the best; this is a nice democratic arrangement but scarcely scientific.

Presumably, the main concern in all examinations of height and weight is the proportion of the body represented by fat. In very emaciated and in very obese persons the principal difference is in the amount of fat, and this may be roughly gaged by the gross weight. Outside of these extremes, however—and it is precisely with less extreme cases that the real interest lies—the relation of fat to weight is far less exact.

The body fat may be estimated from its specific gravity, taking advantage of the low density of fat.[23] When this is done with a group of ordinary men, with no great extremes of emaciation or obesity, there is no correlation between true fatness and the degree of overweight or underweight calculated from height-weight tables.[24]

11. WEIGHT LOSS IN UNDERNUTRITION

Reliable data on weight losses in famine and chronic undernutrition are remarkably few. The person who is semistarved against his will almost invariably overestimates his prestarvation weight and his weight loss. The same is often true of persons on reducing diets

As noted previously, true ideal weights are not known and it is not possible to define precisely the level at which weight loss or departure from standard average becomes important. Probably deviations of less than 10 per cent below standard average weight-for-height are of small moment per se. On the other hand, a sudden weight loss of as much as 5 per cent may be significant. Weight losses of 10 per cent or more that are brought about in a few months in persons not previously obese involve definite impairment in endurance and working capacity and are associated with adverse changes in personality and emotional status.

In previously healthy young adults weight losses up to about 30 per cent can be tolerated with every prospect of eventual full return to normal with proper rehabilitation care. The lethal level is generally around a 40 per cent weight loss, though instances of losses of 50 per cent of weight, with recovery, have been recorded. In severe semistarvation the true weight loss may be difficult to estimate because of the presence of edema; the foregoing figures are for gross weight, including the ordinary amount of edema. When there are exceptionally pronounced edema and ascites, the lethal point may be reached with weight losses of only 20 to 30 per cent.

The rate at which weight is lost in undernutrition is of consequence. In general, it seems that the more rapid the weight loss the more serious is the disability at equal total weight losses. This is a point of both theoretic and practical interest which deserves special study. Allied to this problem is that of adaptive and compensatory phenomena in persons who are habitually underweight in comparison with ordinary standards.

12. MORPHOLOGY: BONES AND TEETH

The bony structures of the body are relatively resistant to caloric undernutrition. No adverse effect on the formed teeth has been objectively demonstrated in either acute or chronic starvation. The bones, however, are not totally immune from change. Hunger or famine osteopathies have been reported many times in both European and Asiatic persons. Whether the affected individuals are peculiar in one or another respect or may only exhibit a more advanced state of a general tendency is not clear. It is probable that mild degrees of decalcification or other osteopathies are seldom recognized.

Droese [25] pointed out the confusion in the literature on the classification of the osteopathies associated with undernutrition but believed that hunger osteoporosis can be distinguished from hunger osteomalacia and late rickets. At the end of World War I a wide variety of osseous disorders were described from Central and Eastern Europe,[26] including delayed ossification in young women [26a] and multiple spontaneous fractures.[27] All ages were represented, but the incidence was perhaps highest in elderly women.

In World War II osteopathies again were noted in Europe, the most frequently observed form being that in which there are areas of translucency in the cortex of the long bones and spontaneous fractures at points of mechanical strain.[28] Pompen and associates [28b] described 24 cases of what they called "hunger osteopathy." They stated that in all cases the diet had been deficient in calcium, phosphorus, protein and vitamin D, and many of the patients had been indoors for long periods. Though undernourished, these patients were not really starved. This situation is radically different from that of the American prisoners of war in Japanese prison camps who showed roentgenologic evidence of osteoporosis on repatriation; these persons had ample exposure to the sun and frequently ate ground fish bones in prison.[29] Such evidence does not support a belief that either calcium or vitamin D deficiency is essential to the development of hunger osteopathy.

In the Minnesota experiment bone density was studied by Dr. Pauline Berry Mack with elaborate quantitative methods developed at Pennsylvania State College. Evidence of any abnormality in bone density was not seen. It seems probable that hunger osteopathies tend to develop only when the undernutrition is prolonged (for a year or more), and even then there must be other factors operative because the incidence never seems to be exceedingly high in famine populations.

13. MORPHOLOGY: MUSCULAR TISSUES

Muscular wasting is always a prominent feature of severe undernutrition. Experimental studies on animals indicate that, in general, the percentage weight loss of the voluntary muscles is somewhat greater than percentage weight loss of the entire body. Most of this wasting seems to be a result of shrinkage of the individual muscle fibers, but in late stages actual destruction of the cells may occur (Jackson,[6] page 162). Brown atrophy, loss of cross striations and granular degeneration have been described, as well as a reduction in the liposomes (minute fat droplets) and occasional appearance of vacuoles.

Presumably, moderate undernutrition only affects

23. Behnke, A. R., Jr.; Feen, B. G., and Welham, W. C.: The Specific Gravity of Healthy Men: Body Weight Divided by Volume as an Index of Obesity, J. A. M. A. **118**: 495-498 (Feb. 14) 1942. Rathbun, E. N., and Pace, N.: Studies on Body Composition: I. The Determination of Total Body Fat by Means of the Body Specific Gravity, J. Biol. Chem. **158**: 667-676, 1945. Morales, M. F.; Rathbun, E. N.; Smith, R. E., and Pace, N.: Studies on Body Composition: II. Theoretical Considerations Regarding the Major Body Tissue Components, with Suggestions for Application to Man, ibid. **158**: 677-684, 1945.

24. Laboratory of Physiological Hygiene, University of Minnesota, unpublished studies.

25. Droese, W.: Beitrag zur Frage der senilen Osteomalazie und der Hungerosteopathie, München. med. Wchnschr. **85**: 1199-1202, 1938.

26. (*a*) Boehme, A.: Gehauft auftretende Knochenerkrankungen infolge von Unternahrung, Deutsche med. Wchnschr. **45**: 1160-1162, 1919. (*b*) Staunig, K.: Roentgenbefunde bei alimentarer Skelettschädigung, Wien. klin. Wchnschr. **32**: 712-713, 1919.

27. Alwens: Ueber die Beziehungen der Unternahrung zur Osteoporose und Osteomalazie, Munchen. med. Wchnschr. **66**: 1071-1075, 1919. Boehme.[26]

28. (*a*) Burger, G. C. E.; Sandstead, H. R., and Drummond, J.: Starvation in Western Holland, Lancet **2**: 282-283, 1945. (*b*) Pompen, A. W. M.; La Chapelle E. H.; Groen, J., and Mercx, K. P. M.: Hunger Osteomalacie in Nederland, Amsterdam, Wetenchappelijke Uitgeverij, 1946.

29. Hibbs, R. E.: Personal communication to the author.

the mass of sarcoplasm, at least for a time, and full recovery on refeeding should be possible. With more severe starvation, where muscle cells are undergoing actual destruction, it may be thought that full recovery could be brought about only by relative hypertrophy of the remaining intact muscle cells. However, mitoses in skeletal muscle of adult animals have been reported during ample feeding following starvation.[30]

Contrary to the textbooks, heart muscle behaves much like skeletal muscle in starvation. In both acute and chronic undernutrition the heart shrinks in volume and in weight, the loss being nearly in proportion to the total weight loss of the body.[31] In the Minnesota experiment the average gross volume of the heart, at systole, measured from teleroentgenkymograms, decreased 17 per cent when the body weight decreased 24 per cent. Since the starved heart may well eject its blood less completely than the normal heart, the actual tissue loss may be underestimated by this roentgenologic method, but in animals the weight loss of the heart is generally a trifle less than proportionate to the total weight loss.

The position of the heart in the chest is also changed in starvation so that ordinary linear measurements do not give an exact indication of the change in total size. In the Minnesota experiment the major axis of the heart in the standing position was, on the average, 4.4 degrees more vertical in starvation than in the control period.

14. MORPHOLOGY: BRAIN AND NERVOUS TISSUE

It has long been taught that the brain and the heart are somehow "protected" in starvation, so that they do not shrink and waste as do the other soft tissues of the body. In the case of the heart, as has been noted this view is in error. But all evidence is in agreement that the brain, and nervous tissue generally, loses little weight even in severe starvation. This does not necessarily mean, however, that these tissues are really unaffected by undernutrition. Histologic examination reveals atrophy, cloudy swelling, chromatolysis and a variety of degenerative changes in the cells.[32] The explanation of the apparent paradox may be suggested by the general agreement that vacuoles and evidences of edema appear in the nervous tissue. Presumably the weight changes are limited because the gross structure is preserved with replacement of cytoplasm, or even of cells, by water. The changes in the spinal cord are similar to those in the brain and may be even more pronounced in the anterior horn cells.[33] Nor are the peripheral nerves immune to the effects of starvation, though the medullated fibers are only slightly affected, morphologically.[6]

15. SKIN, HAIR AND EYES

Caloric deficiency of more than slight degree tends to produce characteristic changes in the skin and hair, but these are not specifically pathognomonic. The skin becomes thin, dry, scaly, inelastic, pallid and grayish. It is cold and "dead" to the touch and tends to slight cyanosis in cold weather. The appearance suggests old age. Besides these changes, which are generally seen and were striking in the men in the Minnesota experiment, there are other changes which appear with less regularity.

A substantial proportion of persons subsisting on a European type of famine diet exhibit rough gooseflesh-like areas of skin, most often on the extensor surfaces of the thighs and upper arms. The condition resembles the follicular hyperkeratitis and folliculosis sometimes associated with vitamin A deficiency. The causation is puzzling because its incidence is highly variable and does not seem to be clearly related to the state of vitamin A nutrition.[34] This condition did not appear in the inmates of Japanese prison camps in spite of gross dietary deficiencies.[9a]

A remarkable peculiarity of the skin in starvation has escaped serious attention until recently. A splotchy, dirty brownish pigmentation, appearing anywhere on the body but most often seen on the face, was casually mentioned in some old reports on undernutrition but occasioned much surprise when it was frequently seen at the close of World War II.[28a] Most of the Minnesota men exhibited it to some degree. The mechanism of the production of this famine pigmentation is unknown; it is not related to nicotinic acid deficiency or pellagra.

The hair in starvation is usually dry, dull and staring. There are many impressions that hair almost ceases to grow and tends to fall out, but objective evidence is lacking.

There is a characteristic appearance of the eyes in starved persons. They look dull and dead. On closer inspection it is seen that the sclera and cornea are unusually devoid of blood vessels so that the whites of the eyes resemble unglazed procelain. In the Minnesota experiment men even soap solution failed to produce reddening.

16. MORPHOLOGY: BLOOD VOLUME

With the exception of bone and nervous tissues, the formed tissues of the body generally are decidedly diminished in gross bulk in undernutrition. In some respects it is proper to consider the blood as a tissue, and its behavior in comparison with other tissues is of interest. More particularly, it is essential to allow for changes in the gross mass of the blood before evaluating the true meaning of changes in the concentration of the formed elements.

Measurements of the blood volume in relation to the nutritional state are still few in number, and some limitations in the technical methods restrict the conclusions which may be drawn from the data. All present methods refer only to the circulating blood. Although in man the reservoirs of noncirculating blood are small, it is possible that the situation may not be precisely the same in normal and in starved persons. Moreover, when starved and normal persons are compared there is the question as to how the blood volume should be expressed to allow properly for differences in gross body size.

Plasma volume was estimated in 15 inmates of the Belsen concentration camp who had lost something like 30 or 35 per cent of their body weight.[35] In the Minnesota experiment the plasma volume was studied systematically before, during and after starvation.[36] As far as they go, the Belsen data confirm the Minnesota work. Before starvation the Minnesota subjects had an average plasma volume of 3.15 liters, and this amounted to 45.3 cc. per kilogram of body weight. At the end of six months of semistarvation the absolute

30. Jackson,[6] p. 167.
31. Keys, A.; Henschel, A., and Taylor, H. L.: The Size and Function of the Human Heart at Rest in Semi-Starvation and in Subsequent Rehabilitation, Am. J. Physiol. **150**: 153-169, 1947.
32. Jackson,[6] p. 181.
33. Jackson,[6] p. 195.
34. Robinson, W. D.; Janney, J. H., and Grande, F. C.: An Evaluation of the Nutritional Status of a Population Group in Madrid, Spain, During the Summer of 1941, J. Nutrition **24**: 557-584, 1942.
35. Mollison, P. L.: Observation on Cases of Starvation at Belsen, Brit. J. **1**: 4-8, 1946.
36. Henschel, A.; Mickelsen, O.; Taylor, H. L., and Keys, A.: Plasma Volume and Thiocyanate Space in Famine and Recovery, Am. J. Physiol. **150**: 170-180, 1947.

plasma volume had increased slightly to an average of 3.41 liters, but this then represented 59.3 cc. per kilogram of the total body weight.

The absolute plasma volume, then, tends to remain constant or increases slightly in starvation. The associated anemia means that the total circulating blood volume is somewhat reduced, but in proportion to the body weight there is a definite blood plethora. These changes are slowly reversed in subsequent rehabilitation; the Minnesota men were fully restored in this respect in about three months.

The behavior of the blood volume in the terminal stages of the most severe starvation may be more complex. Some famine victims die in obvious shock with all signs of severe dehydration; the persistent diarrhea often seen in these cases may produce dehydration, sharp reduction in blood volume and shock as in cholera.

17. MORPHOLOGY: BLOOD CELLS

Some degree of anemia is invariably observed in persons who have undergone prolonged semistarvation. In Asia severe anemia is frequently seen in such persons, but this is probably mainly a reflection of the effect of malaria and other blood-destructive conditions.

In the Minnesota experiment the diet, like European famine diets, was not deficient in iron but there was a progressive moderate anemia in every man during semistarvation. Beginning with an average of 15.1 ± 0.88 Gm. per hundred cubic centimeters of blood in the control period, the average value declined to 12.6 ± 0.80 Gm. after 12 weeks of semistarvation (15 per cent weight loss) and to 11.7 ± 0.80 Gm. at 24 weeks when the weight loss was 24 per cent.[36] These changes are comparable to many observations in famine areas in Europe.

In general, the erythrocyte count and the hematocrit reading change as does the hemoglobin concentration, but the parallelism is not exact. The red blood cells tend to become slightly larger in starvation; the anemia is of the macrocytic type. In the Minnesota experiment the average volume of the red cell, and the content of hemoglobin in it, had increased about 7 per cent at the end of semistarvation.

From the data on plasma volume, the hematocrit reading and the hemoglobin concentration, the total circulating hemoglobin can be calculated. In starvation this is decreased, the decrease in the Minnesota experiment being almost exactly in proportion to the decrease in gross body weight.[36]

The cause of the anemia in undernutrition is not clear; iron deficiency is not primarily responsible. Sternal marrow examinations so far have not provided the answer. Increased, decreased and normal degrees of erythropoiesis have been found in the marrows of anemic starving persons. The possibility that excessive peripheral destruction of the red blood cells is involved is suggested by reports of hemosiderin deposits in the tissue.[37]

In comparison with the rather large variability of leukocytes in normal subjects, the changes in starvation are ordinarily not dramatic. A definite but moderate leukopenia is the rule except where there is intercurrent infection. In the Minnesota experiment the mean leukocyte count was 6,346 per cubic millimeter in the control period and at the end of semistarvation it was 4,129, a decline of 34.9 per cent (see also Zimmer[8]). Correcting for the change in total blood volume, the decrease in total circulating leukocytes averaged 24.1 per cent.

The composition of the leukocytes by types in semistarvation and in fasting has been reported many times in the older literature, but no consistent picture emerges. Several workers found an apparent relative lymphocytosis,[38] but this was not observed in the Minnesota experiment.

In rehabilitation following prolonged undernutrition the correction of the anemia takes place slowly even when protein and iron are supplied in abundance. In the Minnesota experiment the hemoglobin concentration only recovered slightly in 12 weeks and was still appreciably below the control values at 20 weeks when the body weight had been regained; 3 months later, however, (i.e., a total of 8 months after the end of semistarvation), the blood was normal.

18. THE GASTROINTESTINAL TRACT

Gastrointestinal disorders are almost invariably reported from famine areas and frequently contribute greatly to the disability and death of famine victims. Diarrhea and dysentery are always major factors in famine mortality in India,[39] and were prevalent in Europe in both World Wars.[40] The majority of internees and prisoners of war in the Japanese camps in World War II suffered from diarrhea.[9a] In such situations, however, there is a breakdown of sanitation or recourse to strange and peculiar materials as food, or both, so that it is impossible to assess the effects of undernutrition as such.

Attempts to isolate specific pathogens from the stools in most of these cases have been conspicuously unsuccessful. If organisms in the intestine are responsible it must be concluded that forms which normally are not pathogenic may interfere with the function of the intestine of the starving man. Famine victims usually eat anything and everything they can get, and this often means the consumption of irritating, indigestible and spoiled foods, so that nonspecific diarrhea would not be surprising except for its severity.

In the Minnesota experiment, in which strict sanitation was maintained and bad or questionable items of food were never used, diarrhea did not occur at any time though the degree of starvation was comparable to that in the field where diarrhea is so pronounced. This would seem to prove that starvation alone is not causative.

Extreme pathologic changes are often found in the intestinal mucosa of famine victims. These changes may explain the diarrhea in a sense, but the tissue changes are probably the resultant of several factors, of which caloric undernutrition is only one. Certainly starvation produces degenerative changes in all the tissues of the gastrointestinal tract as elsewhere in the body. Additional insult may then easily produce a variety of disorders. An increase in peptic ulcer is commonly noted in periods of undernutrition.[41]

The course of the digestion as affected by starvation is an important question in devising relief programs. In the spring of 1945 it was at first thought that many

37. Lubarsch, cited by Luisada, A.: Beitrag zur Pathogenese und Therapie des Lungenödems und des Asthma cardial, Arch. f. exper. Path.u. Pharmakol. **132:** 313-329, 1928.

38. Bigland, A. D.: Oedema as a Symptom in So-Called Deficiency Diseases, Lancet **1:** 243-247, 1920. Benedict, Miles, Roth and Smith.[1]

39. Aykroyd, W. R.: Nutrition and Health, Indian M. Rec. **59:** 113-116, 1939. Porter.[3]

40. Debray, C.; Zaracovitch, M.; Ranson, B.; Jacquemin, J.; Robert, G., and Siraga, M.: Contribution a l'étude de la pathologie des déportés, Semaine d. hôp. de Paris **22:** 863-870, 1946. Brozek, Wells and Keys.[12] Burger, Sandstead and Drummond.[28a]

41. Magee, H. E.: Application of Nutrition to Public Health: Some Lessons of the War, Brit. M. J. **1:** 475-486, 1946.

famine victims in Europe would require intravenous alimentation, but this proved undesirable in trials in the Netherlands and later in the Belsen concentration camp. Frequent feedings of easily digested foods usually bring about rapid improvement; when this is not the case even the most careful intravenous management may be unsuccessful. The critical point may be indicated by dysphagia. If the patient still feels the pangs of hunger and wants to eat, even a rough and ready feeding program with plain foods will suffice; if the appetite is gone the prognosis is bad (except in anorexia nervosa).

In the Minnesota experiment there were few indications of digestive impairment and no complaints on this score. Gastric acidity (fasting and after histamine) was substantially normal. Gastric motility (rate of evacuation of a test meal) was slightly but consistently depressed.

19. THE BASAL METABOLIC RATE

The basal metabolic rate always represents a large fraction of the total metabolism so that its relation to the caloric intake is a major determinant in the caloric balance. Under normal conditions the basal metabolic rate of the individual is relatively fixed and differences between persons of the same age and sex are considered to be dependent on body size and on the activity of the thyroid gland. It is generally believed that habitual differences in food intake and relative obesity in normal persons have little or no effect on the basal metabolic rate. Persons who are habitually thin, even to a decided degree, apparently have a normal basal metabolic rate when this is expressed per unit of body surface.[42]

When the food intake is sharply reduced below the habitual level for the subject the basal oxygen consumption promptly declines, and this alteration tends to be progressive if the inadequate diet is continued; the absolute change is large. The 32 men in the Minnesota experiment had an average basal consumption of 229 cc. per minute before starvation. After 12 weeks of the famine diet, when the body weight had fallen 15 per cent, this had decreased to 155 cc. and after 24 weeks the average was 139 cc. per minute; a loss of 24 per cent in body weight was associated with a drop of 39 per cent in the basal oxygen consumption. These data, which extend and confirm earlier results, are of obvious practical significance. When subsistence is maintained at a calorically deficient level the progress of the undernutrition itself progressively decreases the caloric deficit so that there is a tendency toward adaptation or compensation.

The absolute changes in the basal metabolism raise questions about the mechanisms involved and the intensity and character of the metabolic processes in the metabolizing tissues. These changes are not merely a reflection of changes in the body surface which would be predicted from the so-called surface law. In the Minnesota experiment, for example, there was an average drop of 28 per cent in the oxygen consumption per square meter of body surface. Subnormal values for the basal metabolic rate, expressed in units of body surface, are universally found in famine areas.

Analysis of these data suggests the need for renewed scrutiny of the surface law. As the body shrinks in starvation the surface increases relative to the tissue mass so that, other things being equal, there would be a greater heat loss and a lower point of temperature equilibrium. The lowered body temperature in turn would retard the enzymatic processes which constitute the metabolism. Although such a chain of events undoubtedly operates, it is not possible to explain the total metabolic alterations on this basis. The decline in body temperature is exceedingly small; in the Minnesota experiment it fell less than 1 degree (F.) in 24 weeks. As a matter of fact, the theory of a heat exchange basis for the surface law is no longer seriously entertained. Changes in peripheral blood circulation readily control the body temperature in the face of great changes in heat production and external temperature.

An important problem is the behavior of the metabolic rate per unit of metabolizing tissue. A first approximation is obtained by expressing the metabolic rate in relation to gross body weight. In the Minnesota experiment the basal oxygen consumption per kilogram of body weight declined 15 per cent in semistarvation. But the gross body weight is not necessarily a reliable index of metabolizing tissue. Fat, bone mineral and extracellular water clearly have little or no metabolic activity. In starvation the proportional composition of the body is changed, there being a relative reduction in fat and relative increases in bone mineral and extracellular water. When allowance is made for these differences, which is possible with the Minnesota data, the apparent alteration in metabolic intensity is reduced but the values are still about 10 per cent below the prestarvation control. In other words, prolonged severe undernutrition produces a small but seemingly significant drop in the basal metabolic rate per unit weight of active tissue (body weight less weights of fat, bone mineral and extracellular water).

In rehabilitation following undernutrition the basal metabolic rate rises more or less parallel to the dietary intake and the gain in body weight. Before body weight is fully restored, however, and for some weeks or months thereafter, the basal metabolic rate surpasses the value which was characteristic of the subject in the prestarvation state. This is particularly clear when the basal metabolic rate is expressed per unit of active tissue or per unit of body weight less fat. In the latter terms the average for the men in the Minnesota experiment after 20 weeks of refeeding, when body weight had been restored, was 13 per cent above their own normal metabolic rates.

20. TOTAL ENERGY METABOLISM

The total energy metabolism is made up of the basal metabolic rate, the specific dynamic action (some 10 per cent of the basal metabolic rate), and the cost of muscular movement and tonus in excess of the basal state. In starvation or severe undernutrition the basal metabolic rate is sharply diminished, as previously noted. Presumably there is also a proportional reduction in the specific dynamic action. The other items in the total metabolic picture are also much reduced.

The energetic efficiency of muscular activity is substantially unaltered in undernutrition except in the most extreme states where gross incoordination may interfere. The energy cost per kilogrammeter of external work like walking and bicycle riding is practically unaltered. This simplifies the analysis.

A large part of the energy cost of muscular work is entailed by moving the body or its parts. In locomotion the work done is simply proportional to the body weight. It follows, then, that the metabolic cost of muscular work is reduced in starvation because of the

42. Blunt, K.; Nelson, A., and Oleson, H. C.: The Basal Metabolism of Underweight Children, J. Biol. Chem. **49**: 247-262, 1921. Strang, J. M.; McCluggage, H. B., and Brownlee, M. A.: Metabolism in Undernutrition: Its Changes During Treatment by High Caloric Diet, Arch. Int. Med. **55**: 958-978 (June) 1935.

reduction in weight of the body and its movable parts. For the majority of activities the reduction in work energy may be considered roughly proportional to the loss in body weight.

Perhaps even more important in most natural life situations is the fact that voluntary activity is greatly diminished in severe undernutrition. Energy expenditure is automatically curtailed and the starving man tends to be immobile, to move slowly when movement is necessary and to assume postures which are most conservative of energy.

The combined effect of all these factors is a large reduction in energy expenditure. In the Minnesota experiment the daily total energy expenditure at the end of semistarvation was only about half that in the control period, in spite of the fact that a fixed occupational and exercise program was maintained throughout. In severe natural famine the reduction in energy expenditure may be considerably greater, so that caloric balance may be achieved at surprisingly low figures. The caloric deficit is apt to be grossly overestimated when calculated simply from caloric intakes.

During nutritional rehabilitation the return of a sense of well-being is coupled with an increase in voluntary physical activity, but the habit of energy conservation is not quickly broken. An effort of will or coercion is often necessary to promote recovery in physical fitness by exercise. The total daily metabolism tends to lag behind the proportional change in the basal metabolic rate in recovery.

21. THE CARDIOVASCULAR SYSTEM

The response of the cardiac musculature to undernutrition has been mentioned in section 13. Changes in cardiac and circulatory function are obvious and in some respects more dramatic.[31] It is well known that both total fasting and prolonged undernutrition tend to produce bradycardia and hypotension in rest. The significance of these changes and other details of circulatory function have received little attention until recently.

Starvation bradycardia is obvious in all instances except where there are extremely powerful heart-accelerating forces at work, such as systemic infection, great excitement or fear, or impending circulatory collapse. From the literature the impression is gained that the bradycardia is perhaps most profound in the earlier stages of severe undernutrition; certainly the degree of bradycardia is not simply related to weight loss. This was also indicated in the Minnesota experiment where the subjects' average basal pulse rate of 34.9 per minute after 12 weeks rose to 37.8 after 24 weeks of semistarvation.

The contrast with beri-beri heart is important. In beri-beri, there may be resting bradycardia but small physical exertion produces decided tachycardia. In simple starvation, exercise produces an increase in the heart rate but this is not disproportionate to the resting rate.

The bradycardia of starvation does not involve heart block; the rhythm is of the sinus type.[43] The rhythm is remarkable for its great regularity; the variability of the length of the P-R interval is smaller than normal in both absolute and relative terms. The electrocardiogram in a state of severe undernutrition shows peculiarities in almost every item of measurement,[43b] but the amplitude changes are most striking. The voltages of all deflections are reduced, particularly the P waves and the QRS complex.

Both systolic and diastolic blood pressures are reduced by undernutrition but these changes, unlike the bradycardia, are moderate and progressive. In severe chronic undernutrition the systolic blood pressure is generally reduced 10 to 30 mm., with a smaller drop in diastolic pressure; the pulse pressure is invariably narrower.[31] These changes have interesting relations to problems of hypertension.[44]

The total circulatory function in starvation is, superficially at least, well preserved. Though there is a tendency to slight peripheral cyanosis, there are usually no complaints referred to the heart and no signs of impending or actual failure except in the terminal state. Nevertheless, detailed analysis indicates that the margin of safety is reduced and that the rate of circulation per unit of metabolic rate is substantially lowered.[31]

In starvation it is common to observe fainting and giddiness, particularly in the upright posture. It is surprising, therefore, to note that no inadequacy of circulatory adjustment to posture is revealed by tilt-table tests.[45]

The restoration of cardiocirculatory function to normal by refeeding does not necessarily follow a simple path of reversal of the starvation changes. When the rehabilitation diet is abundant there may appear signs of relative cardiac insufficiency at the time when the rate of gain of weight and of the basal metabolic rate are at their peaks. The pulse rate, in both rest and exercise, and the venous pressure tend to exceed normal control values, and even frank congestive failure may intervene.[31] The sudden rise in the basal metabolic rate in rehabilitation may produce an intolerable strain on the heart. Full restoration of the heart is not as readily achieved as is the body weight.

22. STRENGTH AND COORDINATION

All psychomotor functions deteriorate in caloric deficiency, and the result is a serious impairment in working capacity. Simple muscular strength, as measured in a single maximal exertion, declines steadily but not as dramatically as does the capacity for continued muscular exertions (endurance). In the Minnesota experiment the single-effort strength of hands, arms and back declined about 30 per cent and the endurance in severe work which produces exhaustion in a few minutes fell as much as 85 per cent. Collapse in the latter tests appeared to be due to muscular failure instead of the circulatory-respiratory type seen in normal persons.

Neuromuscular coordination is impaired by caloric undernutrition, but the relative deterioration is less than in purely muscular capacity.

The psychomotor functions are only slowly restored by refeeding. When the body weight has been regained, there may still persist a serious reduction in muscular endurance. In young men full recovery in these respects takes the better part of a year.

23. THE SPECIAL SENSES

Simple caloric starvation seems to have no deleterious effects on the special senses. In the Minnesota experiment visual acuity was unaffected and there was no evidence of alteration in the senses of touch, taste and smell. Auditory acuity is ordinarily slightly improved

43. (a) Cardozo, E. L., and Eggink, P.: Circulation Failure in Hunger Edema, Canad. M. A. J. **54:** 145-147, 1946. (b) Simonson, E.; Henschel, A., and Keys, A.: The Electrocardiogram of Man in Semi-Starvation and Subsequent Rehabilitation, Am. Heart J., **35:** 584-602, 1948.

44. Brozek, J.; Chapman, C. B., and Keys, A.: The Effect of Semi-starvation on Cardiovascular Dynamics in Normotensive and Hypertensive Persons, J. A. M. A., to be published.

45. Taylor, H. L.; Henschel, A., and Keys, A.: The Cardiovascular Response to Posture and the Problem of Faintness and Syncope in the Semi-Starved Individual, Am. J. Physiol. **152:** 141-149, 1948.

at all frequencies; this was clearly demonstrated in the Minnesota subjects and is confirmed by less objective methods from famine areas. The cause of the sharpened hearing may be mechanical, associated with an enlargement of the free space in the auditory canal. The improvement in hearing is lost during nutritional rehabilitation.

24. INTELLECTIVE FUNCTIONS

Starving persons are ordinarily averse to any effort, including that of the intellect, and their preoccupation with food and their own plight may give an impression of stupidity or mental incapacity. Actually, however, there is no evidence for a decline in basic intellective capacity. In the Minnesota experiment exhaustive studies on memory, reasoning power, verbal and arithmetical facility, and so on, revealed no changes in spite of the subjective impression of most of the men that their mental powers had been reduced.

25. PERSONALITY AND EMOTION

Severe caloric inadequacy produces profound changes in the personality and the subjective state.[46] Externally, the major characteristics are apathy, depression and introversion. Social contacts are avoided and sex interest declines sharply. Psychiatric methods reveal, besides the depression, a well defined rise in the tendencies to hypochondriasis and hysteria. Though the behavior is almost never aggressive, it is easy to discern a tendency to a heightened irritability. The behavior which would ordinarily be associated with increased irritability is suppressed by the overwhelming physical lethargy.

It is difficult to appreciate the enormous preoccupation of the starving man with food and eating. His thoughts tend to be exclusively dominated with these concerns. Their expression may range from constant day-dreaming about eating to extensions such as interest in scientific agriculture. Niceties of behavior are brushed aside where they interfere with the full expression of these interests. Even when the food supply is restored the concern about food persists for many months; a common expression is food hoarding, even when there is not the slightest reasonable basis for this.

Emotional crises and seriously disturbed behavior may arise from the conflict between the concentration on food and previously fixed convictions.[46b] While these may result in irritated or antisocial behavior or even lead to self-destructive impulses, they do not partake of the character of the true psychoses.

Personality changes in refeeding may be even more complex; certainly the behavior may be more variable. As the physical state improves the tendencies toward depression and hypochondriasis diminish, but they may be returned in force by disappointment in the rate of recovery or threats of renewed food restrictions. The return of physical vigor allows outward manifestation of formerly suppressed irritability. At this stage these persons are far more difficult to manage and maintain in an orderly social structure than when they were physically deteriorating. These facts obviously have great sociologic importance.

26. UNDERNUTRITION AND RESISTANCE TO INFECTION

There is no aspect of undernutrition about which there is a more fixed common belief—and less objective evidence—than the question of the effect on resistance to infection. The historical association of famine and pestilence has been so uncritically accepted as indicating cause and effect that there is a dearth of actual research and analysis. The whole problem of nutrition and infection is enormously complicated;[47] obviously no broad generalizations are possible.

Properly, each infectious disease should be considered separately. However, only in the case of tuberculosis is there an appreciable amount of acceptable information. Tuberculosis is discussed separately (section 27); here the other problems are noted briefly. The evidence, such as it is, concerns: (1) indirect suggestions from antibody titers, precipitins, gamma globulin and the like; (2) animal experiments involving experimental infection; (3) casual observations on natural infections in animals; (4) clinical reports, and (5) morbidity and mortality data from famine areas.

A long series of papers from Dr. Paul Cannon's laboratory has stressed the importance of nutrition, particularly protein nutrition, in antibody formation.[48] Most of these animal experiments involved both severe caloric and protein deficiencies, the latter being more drastic than usually seen even in severe famine. The exact relevance of these observations to human caloric deficiency is uncertain; the data themselves are contrary to some older studies.[49]

Experimental studies with injections of micro-organisms into animals in various states of nutrition have been few and of indifferent quality. Opposing observations make it clear that no general conclusions are possible so far (e.g., Edwards[50] versus Robertson and Tisdall[51]). Reports on the incidence and course of natural infections in underfed animals are similarly at variance.[52]

Clinical records may be used to support or to oppose the claim that caloric deficiency, per se, produces a decreased resistance to infection. Some interesting recent data have to do with clinical experience in hospitals associated with prison camps in World War II where surgical procedures were often performed on persons in a deplorable nutritional state without unusual complications.[53]

Morbidity and mortality records from World War II provide material for thought. In contradistinction to previous wars, pestilence was never rampant except where sanitation control was neglected. No epidemics appeared in Western Holland or Greece at the times when there was mass starvation in those areas. The diphtheria epidemic of 1946 appeared to affect the American occupation troops just as severely as the underfed populace. Markowski[54] stated that typhus mortality was worse among the German guards than among the starving Russian prisoners at Hammerstein.

46. (a) Franklin, J. C.; Schiele, B. C.; Brozek, J., and Keys, A.: Observations in Human Behavior in Experimental Semi-Starvation and Rehabilitation, J. Clin. Psychol. **4:** 28-45, 1948. (b) Schiele, B. C., and Brozek, J.: Experimental Neurosis Resulting from Semi-Starvation in Man, Psychosom. Med., **10:** 31-50, 1948.

47. Schneider, H. A.: Nutrition and Infection, the Strategic Situation, in Harris, R. W., and Thimann, K. V.: Vitamins and Hormones, New York, Academic Press, Inc., 1946, vol. 4, pp. 35-70.

48. Cannon, P. R.; Wissler, R. W.; Woolridge, R. L., and Benditt, E. P.: The Relationship of Protein Deficiency to Surgical Infection, Ann. Surg. **120:** 514-525, 1944. Cannon, P. R.: The importance of Proteins in Resistance to Infection, J. A. M. A. **128:** 360-362 (June 2) 1945; The Relationship of Protein Metabolism to Antibody Production and Resistance to Infection, in Anson, M. L., and Edsall, J. T.: Advances in Protein Chemistry, New York, Academic Press, Inc., 1946, pp. 135-154.

49. Zilva, S. S.: The Influence of Deficient Nutrition on the Production of Agglutinins, Complement and Amboceptor, Biochem. J. **13:** 172-194, 1919.

50. Edwards, J. T.: Discussion on Nutrition and Its Effects on Infectious Disease, Proc. Roy. Soc. Med. **30:** 1046-1051, 1937.

51. Robertson, E. C., and Tisdall, F. F.: Nutrition and Resistance to Disease, Canad. M. A. J. **40:** 282-284, 1939.

52. McCay, C. M.: Nutrition, Ageing and Longevity, Tr. & Stud., Coll. Physicians Philadelphia **10:** 1-10, 1942.

53. Gottlieb, M. L.: Impressions of a POW Medical Officer in a Japanese Concentration Camp, U. S. Nav. M. Bull. **46:** 663-675, 1946.

54. Markowski, B.: Some Experiences of a Medical Prisoner of War, Brit. M. J. **2:** 361-363, 1945.

On the whole, the evidence to date suggests that there are various relations in different animals and with different organisms, that the old association of famine and pestilence was largely due to sanitary faults and that in man caloric deficiency is not necessarily productive of a lowered resistance or a heightened susceptibility to infectious diseases in general.

27. TUBERCULOSIS

As far into the past as there are records it is clear that tuberculosis has always increased in periods of severe food restriction. The evidence for the period of the first World War is particularly valuable because it is possible in some cases to dissociate the factor of food shortage from those of overcrowding, excessive labor, sanitation and medical care. The data from Germany [55] are useful, but the analysis of Faber [56] for the situation in Denmark is most significant.

Denmark's domestic food consumption in World War I decreased and then increased owing to the blockade. The housing situation became extremely bad after the food supply was maintained at a good level. Medical care was well maintained at all times. Sharp changes in tuberculosis mortality were closely related to the level of food consumption and were relatively independent of overcrowding, unemployment and the like.

The data from World War II are adding much confirmation to the conclusion that tuberculosis morbidity and mortality are increased by caloric deficiency.[57] In some cases changes in ascertainment distort the figures,[41] but the general picture is convincing. Clinical reports from areas of food shortages emphasize the frequency of a fulminating type of the disease. Tuberculosis is certainly a most serious problem under any circumstance when there is a prolonged severe food shortage.

28. UNDERNUTRITION AND NEOPLASTIC DISEASES

It is now well known that the incidence, growth and recurrence of several types of tumors in animals can be reduced or even prevented by exceedingly severe undernutrition.[58] The prophylactic and therapeutic possibilities of caloric restriction in man have been argued,[59] but there are serious difficulties in application. In animal experiments inhibition of tumors has required the use of dietary levels so low as to retard growth greatly and to prevent estrus.[60] While such levels are reached in human famine, there are no data to show any important effect on the incidence or course of cancer in man. The most that may be said is that the mortality statistics from starvation periods (e.g., in Greece and the Netherlands) do not indicate any increase in cancer; the number of deaths ascribed to neoplasms is reduced in proportion to the total deaths.[11]

29. HYPERTENSION AND CORONARY DISEASE

It has been noted (section 21) that caloric undernutrition normally produces a fall in the blood pressure. What effect this may have on the incidence and course of hypertension and vascular diseases in general is an intriguing question. There are many clinical impressions which are suggestive, but these have little objective basis. Mortality data from famine areas are of limited value because of the problems of certification; in most cases the figures are only grouped under such broad headings as "cardiovascular disease."

The hospital records of Leningrad during the siege of 1941-1942 and after are interesting. In this period of severe food shortage the hospital admissions for hypertension remained at about the ordinary level but the deaths from such conditions dropped sharply.[44] After the food supply was restored to much better levels there was a veritable epidemic of hypertension and coronary deaths in Leningrad. Transient hypertension during refeeding was also noted in the Far East.[61] There is clearly an important area for research here.

30. UNDERNUTRITION AND DIABETES

The association of diabetes with obesity and the advantage of food restriction in this disease are well established.[62] These general relations are reflected in substantial changes in morbidity and mortality from diabetes during periods of food shortages even when these are not productive of real starvation.[63] An improvement in the clinical condition of patients with established diabetes is quickly apparent when the food supply is restricted. Beckert [64] compared 604 diabetic persons in Dresden in the summer of 1939 and again in the summer of 1940. A loss in weight was recorded in 62.2 per cent. Clinically, 45 per cent were improved and only 5 per cent were worse. In Belgium, moderate food shortages in the first three years of World War II were associated with a notable diminution in diabetes morbidity and a more favorable clinical course of this disease.[65]

31. FAMINE EDEMA

Famine (hunger or war) edema was in a sense "discovered" in World War I, though it had been casually observed throughout the ages. The simulation of this condition by protein depletion and a variety of evidences supporting Starling's theory of the role of colloid osmotic pressure in fluid balance led to almost universal belief, in spite of unheeded objections,[66] that famine edema is simply a result of hypoproteinemia. World War II, however, contributed an unexpected denouement.[67]

In starved persons edema may appear with relatively normal values for plasma protein concentration and the albumin fraction is not necessarily decreased. Furthermore, though on the average there may be some relation between the plasma protein level and the extent of the edema, the relation is extremely rough and does not hold for individuals.[68] Cardiac failure is not involved, and the venous blood pressure is actually lower than normal. Finally, it should be noted that the edema fluid is extraordinarily low in protein.

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In ordinary cases of edema due to famine the edema is not so much an accumulation of tissue fluid as simply a retention of the prestarvation level of extracellular fluid; the edema tends to be the expression of a relative and not an absolute excess of fluid in the body. It is probable that mechanical factors—elasticity and structure—outside the capillaries are responsible.

The edema is ordinarily only moderate and is of the soft, dependent type, being notable in the face in the morning and shifting to the lower extremities during the day. Ascites is seldom seen except where there is severe anemia, intercurrent infection, heart failure or decided hypoproteinemia. The latter appears when the diet is unusually devoid of protein. The edema itself is not particularly troublesome, but it is a useful rough guide in evaluating the nutritional state in surveys; it is not a reliable or sensitive indicator in the individual. During refeeding it tends to appear and disappear, being affected by exercise and posture as well as the dietary level.

32. PROBLEMS OF REHABILITATION

The problems of nutritional rehabilitation following semistarvation periodically arise in acute form. The practical necessities of relief allow scant opportunity for research, and the factual information is extremely little. In large scale relief operations the limitations of food materials emphasize the distinction between optimal and feasible programs; the criteria must be those of efficiency and economy.

The character of the diet in the preceding period of semistarvation is important. In general, there are vitamin deficiencies to be corrected in Asia whereas in Europe these tend to be much less prominent. The severity of the state of undernutrition is a determining factor. Almost any food items may be used for the majority of an underfed population, but those persons in an extremely depleted state need easily digested food in frequent feedings. Intravenous feeding is seldom desirable or necessary.

Experience in Europe supports the observations in the Minnesota experiment where it appeared that calories in relative abundance are the first need. The Minnesota subjects manifested a rate of recovery closely proportional to the calories supplied; at intakes of less than 2,700 Calories daily, recovery was exceedingly slow and apparently would have required more than a year. In the Minnesota experiment it was found that intakes over 5,000 Calories daily are unnecessary and may be dangerous. In these young men engaged in light activity the optimal level appeared to be something like 3,500 Calories.

With adequate calories supplied in ordinary foods, including breads made with low-extraction flour, the protein intake will normally be 70 Gm. or more per day. At these levels the isocaloric substitution of protein for carbohydrate produced no discernible benefit in the Minnesota experiment. The extra protein supplement was limited to only 20 Gm. a day, but there is no reason to believe that larger amounts would have important effects.

Special vitamin supplements had no effect on the course of rehabilitation in the Minnesota experiment, nor is there any objective evidence of value in the trials in Europe. It is unnecessary to supply vitamin concentrates unless there is clinical evidence of vitamin deficiency and the relief diet itself is a poor source of vitamins.

With the best of diets and rehabilitation treatment, full recovery from severe undernutrition is slow. Body weight is regained long before functional normality is restored. When the undernutrition lasts for many months and the weight loss is between 20 and 30 per cent, it is probable that complete rehabilitation, including restoration of working capacity, is seldom achieved in less than a year in young adults. With older persons a slower recovery must be expected. It is possible that children recover more promptly.

33. LESSONS FROM CONTEMPORARY FAMINE EXPERIENCE

Acute and persistent problems of starvation and food shortages began to be apparent early in World War II. The problems were not new, but their overwhelming nature has focused attention on them so that it should no longer be possible for them to be neglected by nutritionists in favor of the spectacular advances concerning individual nutrients. But this reawakened interest is coming late, so late that years of opportunity for definitive research have been lost. The data gathered in and immediately after World War II are valuable, but they barely touch many points and on others leave confusion and uncertainty.

Many of the accomplishments and the problems recognized but unanswered are indicated in several recent discussions and monographs.[69] These may be examined with profit not only for the facts presented but for the indications of facts not collected, the theories not critically examined and the questions not answered.

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ACCEPTED FOOD

The following products have been accepted as conforming to the Rules of the Council.

JAMES R. WILSON, M.D., *Secretary.*

Vital Foods Corporation, Evanston, Ill. (Distributed by the American Hospital Supply Company, Evanston, Ill.)

TOMAC ORAL PROTEIN SUPPLEMENT, UNFLAVORED, consists of Ca-Sal (casein and lactalbumin), food yeast, lactalbumin, carrageenin and salt.

Analysis (submitted by manufacturer).—Protein (N × 6.25) 67.5%, carbohydrate 16.5%, ash 7.0%, moisture 6.0%, ether extractables 1.0%.

Calories.—3.25 per gram; 92 per ounce.

Use.—For conditions that require an increased intake of protein.

TOMAC ORAL PROTEIN SUPPLEMENT, FLAVORED, consists of Ca-Sal (casein and lactalbumin), lactalbumin, food yeast, sugar cane, carrageenin and flavor.

Flavoring.—Imitation powdered maple flavor, or pure lemon flavor with citric acid.

Analysis (submitted by manufacturer).—Protein (N × 6.25) 61.5%, carbohydrate 26.5%, ash 6.2%, moisture 5.1% and ether extractables 0.7%.

Calories.—3.25 per gram; 92 per ounce.

Use.—For conditions that require an increased intake of protein.

Sharp & Dohme, Incorporated, Glenolden, Pa.

"DELCOS" PROTEIN-CARBOHYDRATE GRANULES, mixture of protein and carbohydrate, with vanillin, coumarin and essential oils as flavoring agents.

Analysis (submitted by manufacturer).—Protein (N × 6.25) derived from milk 50 per cent, and carbohydrate derived from cane, milk and grain sugars 30 per cent.

Calories.—320 per 100 Gm.

Use.—For conditions that require an increased intake of protein.

Maple Island Farm, Inc., Stillwater, Minn.

"VALLE VERDE LECHE EN POLVO" OR "MAPLE ISLAND'S POWDERED WHOLE MILK," a powdered whole milk with vitamin D_2 added in the form of irradiated ergosterol.

Analysis (submitted by manufacturer).—Butterfat 28.40 per cent, protein (N × 6.38) 26.35 per cent, lactose 37.47 per cent, ash 5.78 per cent, moisture 2.00 per cent and 400 U.S.P. units of vitamin D_2 per reconstituted quart.

Calories.—5.10 per gram; 145.00 per ounce.

Use.—Whole milk powder fortified with vitamin D_2 for general use where whole milk or whole milk solids are required.