be satisfied with sugar costing only five cents per 1000 calories at present market prices, or margarine costing about ten cents. If the hunger for protein were unrelated to calories, the average person in this country by eating a pound of cottage cheese could double his daily intake for the price of a gallon of gasoline.

The special value of animal proteins for growth has been emphasized by many studies, but there is no evidence that these foods excel as fuel for mature individuals. Indeed, the statistics indicate that vegetable proteins have equal fuel value since the caloric expenditure in marginal countries follows the total protein rather than the fraction derived from animal sources.

No doubt the meager supply of protein limits growth and vigor in many regions of the world. Milk and other digestible sources of protein are urgently needed for infant feeding. However, the statistics, strongly indicate that in adults the requirements for protein and non-protein calories are interrelated. If we assume that every adult needs a fixed quantity of protein, and try to give protein-rich foods to an adult population without a proportionate increase of calories, especially fat calories, it is probable that we will be disappointed by their refusal of what we have judged to be a needed food.

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Protein Requirements for Hemopoiesis.

Dear Sir:

In your recent issue[1] dealing with "Nutritional Aspects of Blood Formation," Professor Vilter said "so little is known concerning the protein requirements for hematopoiesis in human beings, that no full-dress discussion of the subject was considered to be profitable." The writer considers that our information on this subject for humans is perhaps not quite as inadequate as Professor Vilter indicates.

According to Whipple,[2] experimental studies on dogs indicate that hemoglobin formation takes precedence over the formation even of serum protein, that the body stores must be greatly depleted, and the intake of protein greatly deficient over a long time before delay in hemoglobin formation occurs. Obviously, Whipple had in mind changes consequent on severe and prolonged dietary privation, and not changes in blood volume, etc., arising from minor changes in body weight.

The purpose of this letter is to suggest the following: (1) as a normal accompaniment to loss in weight, hemoglobin production diminishes at an early stage of dietary restriction when body protein stores may be little depleted and when protein intake is not necessarily low; (2) in prolonged severe undernutrition, although circulating hemoglobin mass is greatly reduced, it is probable that the amount does not fall to that level where obvious clinical manifestations would be expected; (3) in severe undernutrition, protein requirements for hemopoiesis are very small in comparison with total body protein mass and protein intake obtaining; and (4) in severe undernutrition, diminished hemoglobin production is due not to deficiency of protein or other nutrients *per se*, but rather to the concomitant low tempo of metabolism prevailing.

Amplifying these points:

(1) Reduction in weight, whether in the obese or in persons of normal weight, is accompanied by a diminution in the volume of total body fluids, including plasma. Since hemoglobin *concentration* does *not* rise during loss in weight, but is maintained, at least initially, it follows that hemoglobin production must be

slowed down at an early stage when neither body protein stores nor protein intake are likely to be limiting factors.

(2) In severe undernutrition such as that present in the group of Indian prisoners of war studied by Walters *et al.*,[3] circulating hemoglobin mass fell to a mean of 345 g, approximately half the normal value. Hemoglobin concentration fell to a mean of 9.8 g per 100 ml, the scatter of values being small. Now in men and women, not suffering from severe undernutrition, observations indicate that the hemoglobin concentration can fall to 6 g per 100 ml or so, with an associated circulating hemoglobin mass of probably less than 270–300 g, before such reduction is clinically obvious.[4] Moreover, in the tropics and semitropics, various reports indicate that hemoglobin concentrations of as little as 2 g per 100 ml with a circulating hemoglobin mass probably less than 100 g, are not unusually rare in patients with severe ancylostomiasis; yet observers have noted with surprise the occasional lack of obvious clinical stigmata in such sufferers. One infers, therefore, from the above and from other published evidence, that in severe undernutrition, hemoglobin mass is probably maintained at a level higher than that associated with marked clinical stigmata.

(3) The daily demand of new protein for hemopoiesis in severe undernutrition may well be less than is usually believed. In the study on the Indian prisoners already mentioned,[3] upon admission, circulating hemoglobin averaged 345 g. Assuming a 1 per cent destruction daily of red cells,[2] then 3.45 g hemoglobin had to be elaborated each day. Concerning body weight and hence body protein mass, average body weight of the Indians was not reported, but that of the grossly undernourished adult male group at Belsen studied by Mollison *et al.*,[5] averaged 44 kg. Now, according to determinations by Mitchell *et al.*,[6] and Widdowson *et al.*,[7] the percentage of nitrogen in adult cadavers is approximately 2.3 per cent, and hence, very approximately, the proportion of protein matter is about 14 per cent. In severe undernutrition, as for example that observed in the Minnesota study,[8] the *percentage* of "active protoplasmic mass" per total body weight is known to increase. However, using the lower proportion merely for purposes of argument, protein mass of the Indian war prisoners averaged about 6 kg. The protein intake of the latter in captivity was about 15–20 g per diem. Hence, in the severely undernourished Indian subjects, calculations suggest that the amount of regenerated hemoglobin required daily was only about 1/1700th, in comparison to the total mass of body protein then prevailing, not, of course, that one considers this mass of autogenous protein even as largely available for metabolic needs. The amount, moreover, was also small, about one-fifth, in comparison to daily protein intake, although the latter was of inferior biologic value. Now the globin, or the amino acids derived from hemoglobin breakdown, are re-used, at least in part. It is therefore apparent that the daily demand of *new* protein for hemopoiesis under the condition described is very small. Certainly the demand is far less than in lactation, where the high quality protein elaborated is wholly nonreturnable, and where, even in severe undernutrition, the yield of milk, although reduced, may still be considerable.[9]

(4) In the gross undernutrition observed in the Indian and Belsen studies,[3,5] (a) *normal* red cells were produced, and (b) there was no therapeutic response of the anemia to liver or iron (indeed, both hepatic and splenic siderosis, was occasionally observed). Bearing these points in mind, also that the demand for new protein in hemopoiesis is very small, it would seem reasonable to consider that delay in hemoglobin production under these severe conditions is not due to protein deficiency or to other specific nutritional deficiencies *per se*, but rather to that decreased vitality of metabolism accompanying sustained and rigorously reduced total food intake. This situation, however, still allows hemoglobin production to be maintained at a level unlikely to add a serious quota of embarrassment to an already poor clinical picture. It may be noted that Whipple,[2] in his studies on dogs, found that hypoproteinemia or anemia *per se* causes no damage to the body mechanism responsible for the production of plasma protein and hemoglobin; dogs could be kept in good health for years.

It might be added that under conditions of lesser deprivation, there is clear evidence that a low protein intake (and that of low biological value) does *not* prevent satisfactory production of hemoglobin. Thus, the hematologic picture of a group of malnourished Chinese blood donors was shown to become normal at the same rate as that of Caucasian donors, provided additional iron was ingested.[10] Again, iron therapy can restore hemoglobin concentrations to within normal limits in persons suffering severely from hookworm infestation, *without* the diet being improved and *without* the ancylostomes being removed.[11] These observations argue against the validity of the popular view that mild protein deprivation may be responsible for low hemoglobin concentrations occasionally observed under such circumstances.

The foregoing strongly supports Whipple's view cited above: indeed, the writer would go further and hazard the opinion that in humans, death from starvation supervenes before hemoglobin production is critically affected.

Now it has been demonstrated frequently that iron can stimulate erythrocytosis, particularly in women, with or without hypochromic anemia, whether pregnant or non-pregnant. While the anemia of severe undernutrition is certainly not of the iron deficiency type, one wonders whether the presence of very high iron reserves *prior* to undernutrition, may perhaps act as a brake on the fall in hemoglobin production consequent to undernutrition. The South African Bantu lend themselves well for testing this speculation, the main features of their iron picture being as follows:[12]

The iron intake of the adult Bantu is unusually high, as much as 200 mg per day: such iron is largely adventitious and derived from utensils used in food preparation; the uptake of the element is particularly marked with the traditional fermented cereal foods (pH 2–3), which are consumed very frequently and in large amounts. At necropsy, abnormal deposition of iron is apparent in the tissues of more than half of the adults examined; the distribution differs distinctly from that observed in classic hemochromatosis and transfusional siderosis, and is such as might be expected from oral iron "overload." Values for serum iron and total iron binding capacity are frequently elevated, and occasionally are higher than corresponding values in the two diseases just mentioned. Hypochromic anemia is much less common than would be expected from the nutritional and parasitic conditions prevailing. To throw light on the above speculation, hospital records were examined of 35 Bantu men and 21 women, these subjects being amongst the most severely undernourished and malnourished patients (25–40 per cent underweight) seen at Baragwanath non-European Hospital (1500 beds) during the last five-year period. Among these patients "pure" undernutrition was rare; three-quarters were suffering from pellagra. Mean hemoglobin values, standard deviations, and ranges, after correction (13.5 per cent decrease according to Fitzgerald's Law) for the altitude of Johannesburg (5700 ft), for the 35 men were 13.1 ± 1.2, range 7.0–15.2 g per 100 ml; 37 per cent of the patients had values of 14.0 g or more per 100 ml; for the 21 women, 12.1 ± 0.8, range 6.0–15.2 g. per 100 ml; 48 per cent of the patients had values of 12.0 g per 100 ml or more. Unfortunately, clinical information was inadequate; moreover, the hematologic, biochemical, etc. data available were not determined under research conditions. Nevertheless, it is obvious that some subjects, although grossly undernourished, had unexpectedly high hemoglobin concentrations, certainly higher than values reported in corresponding studies undertaken elsewhere. What one would have wished to have known concerning these people was the precise stressful load obtaining, e.g., liver disease, pellagra, tuberculosis, syphilis, bacterial and parasitic infections, and so forth, as well as values for serum iron, blood volume, etc. In other words, one considers it very desirable to know the *maximum* stressful load, including severe undernutrition, which will still permit the maintenance of hemoglobin concentration within normal limits. The necessary investigational work to acquire such information has been planned, but it will take a considerable time before a satisfactory series of severely undernourished subjects becomes available for study.

The information given in this letter (a) underlines the extraordinary high priority given by the body, even when almost *in extremis*, to hemoglobin production: and (b) suggests that the amounts of the factors required for hemopoiesis may well be smaller than are usually believed, because they must have been contained (at least, the non-storable components) in sufficient amounts in the Bantu patients' meager diet which had been consumed in most cases for several months previously.

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