Reprinted from FEDERATION PROCEEDINGS
Vol. 18, No. 4, December, 1959
Printed in U.S.A.

PROTEIN MALNUTRITION AND INFECTION[1]

NEVIN S. SCRIMSHAW

Institute of Nutrition of Central America and Panama (INCAP), Guatemala, C. A.

BOTH PROTEIN MALNUTRITION and acute and chronic infection are recognized to be serious and widely-prevalent health hazards, particularly in tropical and technically underdeveloped areas of the world. The extent to which each may contribute to the severity of the other receives too little attention, however, in the thinking of specialists in both human nutrition and infectious disease control.

In laboratory animals, protein deficiency induced by plasmapheresis combined with a low protein diet (1–5) or by dietary depletion alone, as discussed later in this paper, has been consistently shown to influence the course of both experimental and natural infections. Nevertheless, nutritionists in the United States and Europe have been reluctant to extrapolate these results to man because they find it difficult to conceive of comparably severe deficiencies occurring in human populations and because experiments with milder degrees of malnutrition in human subjects have frequently yielded inconclusive results. The striking experimental demonstrations that specific nutrient deficiencies may limit the spread of a virus in an animal host have also received undue emphasis, since quite the opposite is true for most other types of infections. Furthermore, secondary bacterial infections are likely to be the final cause of death in most viral diseases which end fatally.

Another major reason why so little attention is currently paid to the relationship between nutrition and infection is the failure to recognize the importance of various infections in precipitating acute clinical malnutrition. The 1955 New York Academy of Science symposium (6) discussed the topic "Nutrition and Infection" almost without mentioning the adverse effect of infection on nutritional status, yet the latter is

[1] INCAP Publication I-132.

of major importance in the epidemiology of a number of clinical deficiency diseases commonly seen in technically underdeveloped areas, including kwashiorkor (7, 8) and keratomalacia (9).

The extensive studies which have been made of kwashiorkor in children in the last decade have contributed greatly to our knowledge of human protein malnutrition. While deficiencies of calories and other nutrients may complicate the clinical and laboratory findings in this syndrome, there is no doubt that the edema, changes in color and texture of the hair, pellagroid lesions of the skin, apathy and anorexia as well as the marked lowering of serum proteins and various blood and tissue enzyme activities are largely a direct consequence of protein deficiency. These signs and symptoms respond initially to treatment with skim milk, vitamin-free casein hydrolyzates and even a suitable mixture of synthetic amino acids (10, 11) although eventually secondary vitamin deficiencies become limiting and interfere with further recovery.

It is important to remember that cases of frank kwashiorkor merely reflect the prevalence of underlying protein malnutrition in a large proportion of the child population in the post-weaning and pre-school years. In graphic terms the occurrence of kwashiorkor is like the protruding tip of an underseas mountain whose vast bulk of protein deficiency lies beneath the surface. Since kwashiorkor is known to occur in over 60 countries or territories and since a varicty of infections are also a serious problem in these same localities, the relationship between protein malnutrition and infection has great importance for large areas of the world. Furthermore, research studies of kwashiorkor represent a particularly good opportunity to determine the nature and importance of these relationships.

Children developing kwashiorkor are not necessarily those receiving the poorest basic diet, but more often ones in whom some added stress has served to aggravate the underlying protein malnutrition common in the child population. There is strong epidemiological evidence to suggest that infection constitutes the most common precipitating stress factor. At the same time a large number of these children die as the consequence of an acute infection which would not ordinarily be fatal to a well-nourished child.

In Guatemala, for example, the age specific mortality rate among children 1–4 years of age is more than 40 times that for the United States. INCAP field studies have indicated that most of the difference is about equally accounted for by kwashiorkor, infectious diarrhea, and systemic infections (12). The latter are not virulent tropical diseases but the infections common to children everywhere—measles, pertussis, chickenpox, and respiratory diseases which in the United States would cause few deaths even if untreated.

The interaction of infection and malnutrition to produce more severe or prolonged disease than would result from either alone may be spoken of as synergism. The opposite type of relationship, antagonism, is confined largely, but not entirely, to specific vitamin deficiencies which in animal experiments hinder the growth of certain pathogenic viruses. In best-known examples of synergism, as used in this sense, malnutrition most probably decreases resistance (increases susceptibility) to an infection by interfering with the mechanisms of acquired rather than natural resistance. Evidence of the widespread occurrence of synergism in the relationship between malnutrition and bacterial, rickettsial, protozoan, and helminth infections as well as the predominance of antagonism in the effect of nutritional deficiency on viral multiplication has been recently reviewed in considerable detail (13). After examining the evidence for the occurrence of synergism between protein malnutrition and a variety of infections and considering some of the mechanisms involved, the authors conclude that far more clinical attention should be paid to the interrelationship between malnutrition and infection. They also emphasize that studies need to be continued in order to determine the mechanisms involved and their relative importance. This knowledge is needed for the assignment of due importance to nutritional and other control measures within public health programs in those tropical and subtropical areas in which both malnutrition and infection are serious problems.

EFFECT OF MALNUTRITION ON INFECTION

The studies demonstrating the effect of protein malnutrition on infection vary greatly in the quality of experimental design and the reliability of their conclusions (13), but leave no doubt that severe protein deficiency has a pro-

nounced effect on many infections in experimental animals. For example, protein deficiency in the mouse was synergistic with infection by *Salmonella* (14–17), *Pneumococcus* (18), *Staphylococcus*, *Mycobacterium fortuitum* and *tuberculosis* (19, 20). *Pneumococcus* in the rabbit is similarly affected (21). In the rat, protein depletion has been shown to increase the severity of infection by *Pneumococcus* (22), *S. typhimurium*, *Corynebacterium* (23), Borrelia (24) and *M. tuberculosis* (25). Work with infections of *Salmonella* (26) and *M. tuberculosis* in rats (27, 28) appear to contradict these findings but the extent of the infections was light and the conditions of these studies did not produce as severe a deficiency as in the other experiments cited. Using diets low in casein and inducing tuberculosis artificially by inhalation, Ratcliffe reported antagonism in the rat (29) and synergism in the guinea pig (30); Ratcliffe and Merrick found synergism in the hamster (31). In the mouse studies of Sengupta (32) and in the human studies of Marche and Gounelle (33), a deficiency of animal protein was synergistic with infection due to *M. tuberculosis*. In the only experimental study involving a Rickettsial infection, protein malnutrition proved synergistic with murine typhus in the rat (34).

Nutritional deficiency is much less likely to be synergistic with viral infections and is often antagonistic (13). Protein deficiency appears to have no effect on Theiler virus in the mature mouse (35, 36) nor on swine influenza in the immature mouse (37). In the mature mouse protein deficiency was initially antagonistic to swine influenza virus, but after two weeks no effect could be detected. Lysine deficiency per se does not appear to influence poliomyelitis in the mouse (38) nor does tryptophan depletion have much effect on the spread of Theiler virus in this animal (36).

It is easier to record the studies of the effect of protein malnutrition on infection than to explain the results. Numerous studies with dogs (4, 5), rabbits (3, 39), rats (1, 2) and mice (40) indicate clearly that under the conditions of severe protein deficiency, antibody formation may be adversely affected. Wohl, Reinhold and Rose (41) demonstrated that patients with disturbance of protein metabolism sufficient to cause low serum albumin show an appreciable impairment of antibody response to typhoid vaccine. Some other attempts to demonstrate this in man (42–45) have failed, presumably due to the relatively mild protein malnutrition in the subjects studied. Of course, resistance to a given disease does not depend exclusively on the anamnestic response. For example, Zucker and co-workers (46) found no relationship between the decreased ability of rats to form agglutinins to a vaccine prepared from killed culture of *Corynebacterium kutscheri* and their resistance to the live organism. The conclusion from the studies of malnutrition and antibody formations in man is not that he differs from other animals in this respect but that sufficiently severe protein deficiencies in man are not readily produced by feeding deficient diets to well-nourished individuals for relatively short periods of time, nor even by the type of depletion usually associated with chronic disease.

Another mechanism of possible importance in the synergism of malnutrition and infection is the effect of nutritional deficiency on phagocytic activity. Guggenheim and Buechler (14, 47) conclude from their work with rats that low protein diets 'invariably' interfere with leucocyte production. It is of particular significance that in these studies peanut protein promoted greater leucocyte regeneration than would be predicted from its effect on growth. This suggests once more that amino acid requirements for different body functions may differ somewhat and that a single reference protein of standard amino acid composition is not likely to be equally good for growth and for antibody formation.

Other possible mechanisms involved are discussed in the review previously mentioned (13). They include direct effect on tissue integrity, interference with non-specific protective substances, non-specific destruction of bacterial toxins, alterations of intestinal flora and changes in the endocrine balance of the host. Children with kwashiorkor provide an unusual opportunity to study the effect of severe protein depletion in man on antibody formation, leucocyte activity, and the various other functions suggested by observations in experimental animals to be of importance in the interrelation of malnutrition and infection.

EFFECT OF INFECTION ON PROTEIN MALNUTRITION

Diarrheal and other infections are exceedingly common among young children in technically underdeveloped areas. A child developing kwashiorkor usually has a history of an infection some weeks before the actual onset of the

edema, skin lesions and other clinical signs of the syndrome (48, 49). Furthermore, the majority of young children in areas in which kwashiorkor is common are suffering from a degree of protein deficiency sufficient to interfere with growth and development and often to produce changes in the color and character of the hair. It has been assumed that diarrhea of infectious origin frequently serves as a precipitating stress by interfering with the absorption of protein and thus is a major factor in the epidemiology of kwashiorkor. The effect of diarrheal infections on absorption, however, may be only a small and incidental part of the mechanism involved. Careful metabolic studies have shown that diarrhea per se does not always interfere appreciably with absorption (50). Furthermore, a variety of other infections not generally associated with diarrhea have been shown to have a pronounced effect on nitrogen excretion. These include erisipelas (51), meningitis (52), malaria (53), pneumonia, pyelonephritis, paratyphoid (54), typhoid (55, 56) and tuberculosis (56, 57).

When any of these infections are present, nitrogen excretion in the urine is invariably increased. Even if fever is present, the magnitude of the influence of nitrogen equilibrium is much greater than could be accounted for by the increase in basal metabolic rate associated with the elevation in temperature (58). It appears that the adverse influence of infection on nitrogen balance is due to actual cellular breakdown or interference with cellular metabolism rather than to either increased utilization or decreased absorption of protein.

Epidemics of kwashiorkor 6–8 wk. after an outbreak of measles have been noted on several occasions (59 and INCAP unpublished data). The degree of cellular damage would presumably be far more widely disseminated in the body in viral infections than in those of bacterial origin. The isolation by Ramos-Alvarez and Sabin (60) of a virus in 40% of children with diarrhea in Cincinnati and our failure in Central America to find a bacterial pathogen in more than 10% of diarrheas in children (59) suggests that viruses may be the most important factor in infectious diarrheas, although direct proof is still lacking.

Infection also contributes indirectly to aggravation of the protein deficiency in malnourished children. The mother, and sometimes the physician, will often withdraw from the diet of the child what few solid foods he may be getting and place him on a diet of thin cereal or corn starch gruel. The mother may also interpret the diarrhea as due to 'worms' and give the child a strong purgative. In fact, one of the important factors to consider in evaluating the effect of infection on nutrition in field studies, is the tendency of the parent to change the diet for the worse in the presence of infection.

The adverse effect of infection on nutritional status is of course not confined to children, but it is most frequently in the pre-school children that previous protein nutrition is so poor and protein reserves so inadequate that the effect is clinically detectable. Certainly some of the consequences of the multiple acute and chronic infections common among people living under unhygienic conditions are a result of their effect on malnutrition rather than the direct effect of the pathogen itself. It is important to bring diarrhea and other diseases under control as promptly as possible because of their effect on nutrition, quite apart from any toxic effects of the disease itself.

SUMMARY

There are many studies which demonstrate that severe protein deficiency may have a pronounced effect on the severity of infections in experimental animals. Nevertheless, the few studies conducted on human subjects have not succeeded in giving convincing evidence on this point, probably because they have not dealt with a sufficiency severe protein deficiency. There is considerable epidemiologic evidence, however, that infections in man aggravate protein malnutrition through their unfavorable influence on nitrogen balance. They also have an indirect effect since they diminish appetite and also frequently cause the parent or even the physician to reduce both the quantity and quality of the diet. There is a dynamic interaction between nutrition and infection which is of special importance to tropical and technically underdeveloped areas of the world where both protein malnutrition and infections are prevalent. To a considerable degree, success in improving health in such areas requires that attention be given to both the control of infections and the improvement of nutrition. Research studies of children with kwashiorkor offer a particularly good opportunity to determine the nature and importance of the relationship between infection and protein malnutrition in man.

REFERENCES

1. Benditt, E. P., R. W. Wissler, R. L. Woolridge, D. A. Rowley and C. Steffee. *Proc. Soc. Exper. Biol. & Med.* 70: 240, 1949.
2. Berry, L. J., J. Davis and T. D. Spies. *J. Lab. & Clin. Med.* 30: 685, 1945.
3. Cannon, P. R., W. E. Chase and R. W. Wissler. *J. Immunol.* 47: 133, 1943.
4 Madden, S. C. and G. H. Whipple. *Physiol. Rev.* 20: 194, 1940.
5. Miller, L. L., J. F. Ross and G. H. Whipple. *Am. J. M. Sc.* 200: 739, 1940.
6. Miner, R. W. (Editor). *Ann. New York Acad. Sc.* 63: 145, 1955.
7. Béhar, M. and N. S. Scrimshaw. *Trans. New York Acad. Med.* In press.
8. Trowell, H. C., J. N. P. Davies and R. F. A. Dean. *Kwashiorkor.* London: Arnold, 1954, p. 64.
9. Oomen, H. A. P. C. *Fed. Proc.* 17, Suppl. 2: 111, 1958.
10. Brock, J. F., J. D. L. Hansen and E. E. Howe. *Lancet* 2: 355, 1955.
11. Hansen, J. D. L., E. E. Howe and J. F. Brock. *Lancet* 2: 911, 1956.
12. Béhar, M., W. Ascoli and N. S. Scrimshaw. *World Health Organization* 19: 1093, 1958.
13. Scrimshaw, N. S., C. E. Taylor and J. E. Gordon. *Am. J. Med. Sc.* 237: 367, 1959.
14. Guggenheim, K. and E. Buechler. *J. Immunol.* 58: 133, 1948.
15. Guggenheim, K. and E. Buechler. *J. Hyg.* 45: 103, 1947.
16. Watson, M. *J. Hyg.* 37: 420, 1937.
17. Watson, M., J. Wilson and W. W. C. Topley. *J. Hyg.* 38: 424, 1938.
18. Sako, W. S. *J. Pediat.* 20: 475, 1942.
19. Dubos, R. J. and R. W. Schaedler. *J. Exper. Med.* 108: 69, 1958.
20. Schaedler, R. W. and R. J. Dubos. *J. Exper. Med.* 104: 67, 1956.
21. Wissler, R. W. *J. Infect. Dis.* 80: 250, 1947.
22. Wissler, R. W. *J. Infect. Dis.* 80: 264, 1947.
23. Miles, J. A. R. *Brit. J. Exper. Path.* 32: 285, 1951.
24. Guggenheim, K., E. Buechler and S. Halevi. *J. Infect. Dis.* 88: 105, 1951.
25. Koerner, T. A., H. R. Getz and E. R. Long. *Proc. Soc. Exper. Biol. & Med.* 71: 154, 1949.
26. Metcoff, J., D. B. Darling, M. H. Scanlon and F. J. Stare. *J. Lab. & Clin. Med.* 33: 47, 1948.
27. Lange, L. B. and N. Simmonds. *Am. Rev. Tuberc.* 7: 49, 1923.
28. Metcoff, J., D. Darling, D. Wilson, A. Lapi and F. J. Stare. *J. Lab. & Clin. Med.* 34: 335, 1949.
29. Ratcliffe, H. L. *Fed. Proc.* 10: 368, 1951.
30. Ratcliffe, H. L. *Fed. Proc.* 13: 441, 1954.
31. Ratcliffe, H. L. and J. V. Merrick. *Am. J. Path.* 33: 107, 1957.
32. Sengupta, S. R. and J. W. Howie. *Brit. J. Nutrition* 2: 313, 1948.
33. Marche, J. and H. Gounelle. *Milbank Mem. Fund Quart.* 28: 114, 1950.
34. Fitzpatrick, F. *Am. J. Pub. Health* 6: 676, 1948.
35. Kearney, E. B., W. L. Pond, and B. A. Plass. *J. Infect. Dis.* 82: 177, 1948.
36. Kearney, E. B., W. L. Pond, B. A. Plass, K. H. Maddy, C. A. Elvehjem and P. F. Clark. *J. Bact.* 55: 89, 1948.
37. Sprunt, D. H. *J. Exper. Med.* 75: 297, 1942.
38. Jones, J. H., C. Foster, W. Henle and D. Alexander. *Fed. Proc.* 6: 411, 1947.
39. Gemeroy, D. G. and A. H. Koffler. *J. Nutrition* 39: 229, 1949.
40. Toomey, J. A., W. O. Frohring and W. S. Takacs. *Yale J. Biol. & Med.* 16: 477, 1944.
41. Wohl, M. G., J. G. Reinhold and S. B. Rose. *Arch. Intern. Med.* 83: 402, 1949.
42. Balch, H. H. *J. Immunol.* 64: 397, 1950.
43. Bieler, M. M., E. E. Ecker and T. D. Spies. *J. Lab. & Clin. Med.* 32: 130, 1947.
44. Havens, W. P., Jr., D. G. Bock and I. Siegel. *Am. J. Med. Sc.* 228: 251, 1954.
45. Larson, D. L. and L. S. Tomlinson. *J. Lab. & Clin. Med.* 39: 129, 1952.
46. Zucker, T. F., L. M. Zucker and J. Seronde, Jr. *J. Nutrition* 59: 299, 1956.
47. Guggenheim, K. and E. Buechler. *J. Immunol.* 54: 349, 1946.
48. Scrimshaw, N. S., M. Béhar, F. Viteri, G. Arroyave and C. Tejada. *Am. J. Pub. Health* 47: 53, 1957.
49. Jelliffe, D. B. *Infant Nutrition in the Subtropics and Tropics.* W.H.O. Monograph Series No. 29. W.H.O., Geneva, 1955.
50. Chung, A. W. and B. Viscorova. *J. Pediat.* 33: 14, 1958.
51. Coleman, W., D. P. Barr and E. F. DuBois. *Arch. Intern. Med.* 29: 567, 1922.
52. Grossman, C. M., T. S. Sappington, B. A. Burrows, P. H. Lavretes and J. P. Peters. *J. Clin. Invest.* 24: 523, 1945.
53. Barr, D. P. and E. F. DuBois. *Arch. Intern. Med.* 21: 627, 1918.
54. Kocher, R. A. *Deutsches Arch. klin. Med.* 115: 82, 1914.
55. Coleman, W. and F. C. Gephart. *Arch. Intern. Med.* 15: 882, 1915.
56. Krauss, E. *Deutsches Arch. klin. Med.* 150: 13, 1926.
57. Rao, B. S. N. and C. Gopalan. *Indian J. M. Res.* 46: 93, 1958.
58. Peters, J. P. and D. D. Van Slyke. *Quantitative Clinical Chemistry.* Baltimore: Williams and Wilkins, 1946, p. 678.
59. DeMaeyer, D. B. Personal Communication, 1958.
60. Ramos-Alvarez, M. and A. B. Sabin. *J.A.M.A.* 167: 147, 1958.