PHYSIOLOGICAL REVIEWS

VOL. XIV JULY, 1934 No. 3

THE INFLUENCE OF NUTRITION UPON RESISTANCE TO INFECTION

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The possibility that diet may have some influence upon the incidence, course, and final outcome of infection, is a comparatively recent idea. Since 1900 the idea has gained ground, and quite a body of work has appeared in the literature. The task of reviewing it is not easy for several reasons: in many cases the results are contradictory, in ethers they may be difficult of interpretation because of many variables At best the literature is a scattered one. In considering the actual infection, the author has confined himself to infections of bacterial origin, and has not included, for lack of space, much excellent and suggestive work on infections of protozoan and metazoan origin.

In general one may say that the work in this field is in its infancy, but that there is much suggestive work that merits further study,

Vitamin B complex. …

Vitamin C. Although the cure of scurvy by diet was known to navigators four centuries ago, the epidemic nature of the disease suggested a bacterial origin to many investigators in the era of Pasteur. There can be no doubt that in man, and in experimental animals, infections of

various kinds may cause a latent scurvy to develop into the outspoken disease. Jackson and Moody (1916) cultivated from organs of scorbutic guinea pigs a green producing streptococcus, which, injected into animals fed on a scurvy producing diet, led to the rapid progression of scorbutic lesions and death. It had little effect on normal animals. This work is an early example of the use of an organism peculiarly pathogenic for the animal studied, during the development of a deficiency disease. It is likely that in guinea pigs, suffering from entire deficiency of vitamin C, and moribund in consequence, almost any form of injury will bring about death. A partial deficiency in the experimental animal might give better results. Findlay (1923) therefore produced a type of chronic scurvy, by giving an inadequate amount of the anti-scorbutic factor, 2 cc. of orange-juice, every third day. Although the guinea pigs were in good general condition, they were found to be very much more susceptible than controls to the intraperitoneal injection of pneumococci, S. aureus, S. hemolyticus, and B. coli. Other authors have shown that spontaneous fatal infections are also much more likely to occur in scorbutic animals. Nicolle (1912) called attention to the frequency of pneumonia which occurred in guinea pigs which were fed on poor diets. Theobald Smith (1913) observed that epidemic pneumonia promptly ceased in his colonies of guinea pigs, when fresh green fodder was provided. The beneficial factor was not identified, and no evidence of latent scurvy was mentioned in these observations. In a study of 400 animals, Wamoscher (1927) showed clearly that subacute scurvy in guinea pigs predisposes to spontaneous pneumonia. The course of the illness was followed by Rontgen-ray. The facts that many of the organisms isolated were not pathogenic for normal guinea pigs, and that cure sometimes followed the use of large quantities of orange-juice, are of great significance. In attempting to induce infection of scorbutic guinea pigs by inhalation of droplets containing B. suipestifer and pneumococcus, Schmidt-Weyland and Koltsch (1927-28) were not always invariably successful. They clearly proved that infection does not take place until the resistance of the animal has fallen very considerably. The scorbutic animals, which were already carriers, as shown previously by nasal cultures, succumbed more frequently than did those in whom the disease was not so far advanced. Injury of the mucous membrane by silver nitrate or by mustard oil, will frequently bring about loss of resistance in normal animals. Scorbutic guinea pigs, infected with Streptococcus hemolyticus, develop lesions very similar to those of rheumatic fever in man (Rinehart, Connor and Mettier, 1934). Many in-

vestigations have been made of tuberculosis in scorbutic animals; see section on *Tuberculosis.*

There can be no doubt that in the guinea pig, scurvy lowers resistance to certain types of infection. The mechanism involved will be considered later.

Vitamin D. …

3. *Vitamin C.* Mouriquand et al. (1923), believed that scurvy and tuberculosis in the guinea pig were without influence one upon the other. Leichtentritt (1924b) discussed the earlier reports, and found that lemon juice prolonged considerably the lives of tuberculous guinea pigs fed on a scurvy producing diet.

Bieling (1924a) produced chronic tuberculosis by inoculating guinea pigs with tubercle bacilli attenuated by treatment with quinine derivatives. Such animals lived for two years, and had well localized lesions in the liver and spleen. Scurvy-producing diets led to the death of such animals in five to eleven days, whereas non-tuberculous controls lived three or four weeks. This experiment was designed to account for the high death-rate of tuberculous persons during periods of bad nutrition in Germany during the war. In this report, Bieling makes no comment on the presence of scorbutic lesions in his animals, nor upon the probable cause of their death, Careful histological examination in a series of animals with more acute tuberculosis (Bieling, 1924b) revealed scurvy in one instance, ten days after the diet was started, but no scurvy in six others. Bieling, however, believes that such animals are to be compared to human cases of "latent" scurvy. He suggests as an explana-

tion, a state of "anergy," basing his view upon the known decrease of the dermal reaction to tuberculin in scurvy as observed by Prausnitz and Schilf (1924). (See also: Sehütze and Zilva, 1927) Although tuberculous scorbutic guinea pigs may have a diminished dermal reaction to tuberculin, they are killed by the injection of doses only ½ to ⅓ of those fatal to non-scorbutic tuberculous guinea pigs (Bieling, 1925). From further reports of Bieling (1924c, d) it appears that the "normal" and "scurvy-producing" diets were different in so many particulars, that the results are not necessarily to be attributed to the absenct of vitamin C. He did not, for example, use a diet for the controls consisting of the scurvy-producing diet *plus* orange-juice. This question bears directly upon the clinical practice of the use of antiscorbutics in the treatment of certain types of human tuberculosis. It could be settled by the analysis of organs by chemical methods (adrenals, especially), for vitamin C; and by the use of pure ascorbic acid.

Heymann (1925) induced subacute scurvy in tuberculous guinea pigs. These animals lived 73 days, the tuberculous controls living 141 days. Death was due to scurvy, rather than to tuberculosis.

The experiments so far discussed deal with animals already tuberculous, in which scurvy is induced some time later. Sewal et al, (1927) have attempted to ascertain whether a diet for guinea pigs, relatively, low in green cabbage, will render the animals more ready to contract tuberculosis by contact with infected animals. Males only were used. Although the 97 animals on the deficient diet contracted pneumonia, they did not appear to contract tuberculosis. No controls on a normal diet were studied. McConkey and Smith (1933) have shown that in the majority of cases, guinea pigs, maintained on a diet low in vitamin C develop ulcerative lesions of the intestine if fed daily doses of tuberculous sputum. If this deficient diet is supplemented by adequate amounts of tomato juice, the animals almost invariably remain free from intestinal tuberculosis. They stated that cod liver oil was not protective. It must be pointed out that guinea pigs require very little vitamin A and that small amounts were undoubtedly present in the basic diet.

Hagedorn (1928) has produced a type of tuberculous disease, unlike that of man, by intraperitoneal injection of 20 mgm. of bovine tubercle bacilli in rats. A basic diet was devised, free of vitamins A and D, B and C. He found that absence of the A and D component (cod liver oil) decreased the time of survival more than did either of the other deficiencies. Vitamin B complex (brewer's yeast) had little effect. Vitamin C (orange juice) had a definite protective effect. It is, however, not

generally believed that rats require vitamin C; and the question is raised by Hagedorn's experiments of the presence in orange juice of some protective activity other than vitamin C. Here again, the actual determination of ascorbic acid in the tissues or its use in feeding is indicated.

4. *Vitamin C.* McConkey (1930) reported that tuberculosis of the intestine is not benefitted by cod liver oil, but is improved by ultraviolet irradiation; a much better result is obtained by the use of cod liver oil and orange juice or tomato juice. This effect may in part be due to the vitamin C. The inferences of Stub-Christensen (1929-31) would seem to indicate the great importance of vitamin C, but no definite proof is given. He observed a rapid decline in the morbidity rate of tuberculosis in Denmark in April, when new potatoes are suddenly introduced into the diet. But as he points out, other dietary factors, especially vitamin A, are likely to be introduced at the same time. It would also seem that respiratory infections which aggravate tuberculosis must be decreasing at this season. So far as the reviewer is aware, no definite study has been made of the use of diets high in vitamin C, but not in other vitamins, for the treatment of tuberculosis. This is remarkable, in view of the evidence supplied by the experimental work with scurvy and tuberculosis in animals.

4. *Vitamin C.* Abels (1924) reviewed earlier work on infection and scurvy; and stated his concept of the "dysergy" of scurvy. One characteristic of this dysergy is said to be lack of resistance to infection. It is evident that during shortage of anti-scorbutic food, when scurvy is frequent in the whole population, infections, especially tuberculosis, are of frequent occurrence (Schagan, 1924). A series of infections occurred in 34 of Rosenbund's cases (1923) *before* scurvy became evident. Possibly these infections precipitated scurvy—as did vaccination in the cases reported by Stern (1923). A vicious circle could then arise. It must, however, be remembered that in infants with scurvy, other deficiencies may exist. Bloch (1928) states that the frequency and severity of infections in scurvy is not much greater than that in any other group of hospital cases—with the exception of those with xerophthalmia.

In infants not definitely scorbutic, Meyer (1925) reported that the tendency to develop repeated infections is greatly lessened by the administration of 50 to 100 cc. of orange-juice a day. Reyher (1925) recorded 24 cases of pyuria, of which 38 per cent died and 29 per cent recovered. In 29 other cases, he administered 100 to 2,00 grams orange-juice and a commercial yeast extract; of these cases 3.4 per cent died and 86 per cent recovered. The second series of cases was studied after the first; the treated and untreated cases were not taken alternately at the same time. Orange-juice undoubtedly contains an active factor other than vitamin C. Debris (1931) thought that lemon juice might in some instances, cure pyuria. He has recently advocated a mixture of all vitamins.

It is clear that infections may be frequent and severe in scurvy, or in the "prescorbutic state." It is not yet known how frequently latent scurvy occurs, nor is it proven that in infants fed on a normal diet, increase of vitamin C will prevent severe infection.

5. *Vitamin A.* …

GENERAL CONCLUSIONS. Susceptibility to infection is not as a rule affected by diet. Resistance to infection, on the other hand, may be greatly reduced by deficient diet. A deficiency in the diet of vitamins A and C appears quite definitely to lower resistance to infection. In certain cases, a lack of the vitamin B complex may also do the same thing; A lack of vitamin D cannot be said to have a proven effect in in lowering resistance. It seems probable that the existence of a partial deficiency of vitamins may result in loss of resistance to infection, though this cannot be said, from the present evidence, to have been clearly established,

The evidence discussed in this paper points to certain lines for future investigation. In the study of the influence of diet upon resistance to tuberculosis, we need to discover methods of producing in experimental animals, a chronic form of the disease like that in man. In the study of human tuberculosis we need a more careful analysis of the effects of minerals, in particular, of sodium chloride, and of the acid and base values of the diet; and of deficiencies of vitamins A and C,

We need a search for the existence of anti-infective substances other than the ones already recognized in natural foodstuffs, e.g., fruit juices. We need the use of highly purified vitamins in experiments designed to study the question of partial deficiencies. We need to use, and perfect, chemical methods for analysis of tissues and foodstuffs. We need a more careful study of tissue reactions in animals suffering from food deficiencies and infections, and finally more carefully planned experiments dealing with partial and multiple deficiencies.

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PHYSIOLOGICAL REVIEWS

VOLUME XIV

BALTIMORE, MD,
1934

CONTENTS

No. 3. JULY, 1934