THE VITAMINS AND RESISTANCE TO INFECTION

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INTRODUCTION

In many of the investigtions on the relation between the vitamins and resistance to infection rations lacking in several essentials have been employed, usually in an effort to test the effect of inadequate human dietaries. Although such investigations have yielded results of practical value, they do not disclose the rôles played by the diverse missing substances. More definite information on this question can be obtained from experiments in which diets deficient in one vitamin only are utilized and the following review has been limited, with very few exceptions, to the discussion of such work. Very numerous papers on this subject have appeared and some no doubt have been overlooked by the author. Wherever possible the investigations have been described in sufficient detail for the reader critically to appraise them. Unfortunately many of the experiments have been carried out on such small numbers of animals that the results are not statistically significant.

The problem of whether the metabolic changes resulting from the deficiency of a vitamin are accompanied by changes in the defense mechanism has been attacked by at least four different methods, as follows:

(1) By the determination of any changes in the natural immune bodies or cellular reactions, due to the deficiency.

(55) See Ref. 50 under "Vitamin A and D."
(56) See Ref. 51 under "Vitamin A and D."
(57) See Ref. 20 under "Vitamin A."
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VITAMIN C

1. Variations in the natural immune bodies or tissue reactions in vitamin C deficiency

(a) Results indicating that these are reduced. Fortenato (1) reported in 1921 that the opsonic index was lower in scorbutic than in normal guinea pigs. In the following year, Leichentritt and Zielaskowski (2) measured the trypanocidal substance in the blood of guinea pigs suffering with scurvy and found that it was reduced. Höjer (3) however criticized the latter's experiments on the grounds that they were carried out on too few animals.

According to Prausnitz and Schilf (4) tuberculous scorbutic guinea pigs show considerably smaller tuberculin reactions, which also dis-

appear more quickly than those in tuberculous guinea pigs subsisting on normal diets. The febrile reaction after the tuberculin injection was also less marked in the scorbutic animals. This reduced skin reactivity was not correlated with a generalized unsusceptibility to tuberculin (5) as the animals with scurvy died more frequently than the normal controls when this substance was injected subcutaneously in large amounts (5 cc.).

In addition, Bieling (6) and also Arkwright and Zilva (7) found that markedly scorbutic guinea pigs gave smaller skin reactions to diphtheria toxin than normal. The former author noted that the necrosis of the skin was slower coming on, and that the subcutaneous oedema was absent or very slight. The latter authors reported that animals on diets which contained suboptimal amounts of vitamin C, but enough to allow a gain in weight of about 25 per cent, still showed large Schick reactions, whereas if this vitamin was further reduced so that a loss of about the same magnitude occurred, the reactions were very small. Scorbutic guinea pigs however are definitely more susceptible to large doses of diphtheria toxin and die earlier than normal animals according to Bieling. A possible clinical application of these findings was provided by Hess (8) in 1932. He had encountered nasal diphtheria very commonly in children with scurvy. The Schick reactions were regularly negative, although the patients showed the bloody mucous nasal discharge which is typical of this disease, and one child apparently died from it. In three cases, virulence tests showed the bacilli to be virulent. The last of these three cases gave no skin reaction to dilutions of from $\frac{1}{50}$ to $\frac{1}{5}$ M.L.D. of toxin. In his brief review the author does not discuss the possibility of these cases being carriers, already self-immunized. He suggests that in scurvy the pharyngeal mucous membrane loses its immunity to the diphtheria bacilli, whereas the general immunity as reflected by the negative Schick test is still maintained. A simpler explanation however might be that the scorbutic skin does not react in the usual manner to the toxin, although the organism as a whole is not immune to it.

Lawrynowicz (9) suggests that scurvy may so reduce the resistance that a carrier may become the victim of bacteria which it previously carried with impunity. For example, a guinea pig that had been well

for one month after it had been used in a crude test for B. diphtheria was placed on a scorbutic diet. Thirty-seven days later it died. The post-mortem showed the changes found in diphtheritic deaths and the organism was recovered from the spleen.

When Vercellana (10) injected strychnine nitrate or aqueous extracts of poisonous fungi subcutaneously into scorbutic guinea pigs, he found that they were killed more frequently by these substances than controls fed normal diets. The ration of the deficient animals consisted of oats exclusively. Also aleuronat, broth, peptone, cinnabar and other substances, when injected by Dluzewski (11) into the peritoneal cavities of scorbutic animals, did not provoke the normal inflammatory reaction with the outpouring of leucocytes.

(*b*) *Results indicating that these are not reduced.* In contrast to some of the above findings, Lawrynowicz and Bohdanowicz (9) state that they have never established any difference between the Schick reactions of normal and scorbutic guinea pigs.

In 1919, Zilva (12) determined the complement titres in normal and scorbutic guinea pigs and found that they were the same. Four years later, Hamburger and Goldschmidt (13) reported that the complement titres were not lowered in scorbutic children and guinea pigs. In fact, some of the latter animals showed increased complement titres, which were apparently correlated with high albumin concentrations in the serum. Koch and Smith (14) found consistently increased complement titres in a series of twelve scorbutic guinea pigs. When an antiscorbutic was added to the diet, the titres fell, but still remained somewhat higher than they had been before the onset of the scurvy. On the other hand, Bohdanowicz and Lawrynowicz (9) found that complement did not show any constant or characteristic changes in guinea pig scurvy.

The phagocytic indices in scorbutic guinea pigs were reported by Werkman et al. (15) to be unaltered.

Hamburger and Goldschmidt (13) also determined the bactericidal titres of the sera of scorbutic and normal guinea pigs and of scorbutic and normal children to the same strain of colon bacillus and found that they were similar. This organism was used because the pyelonephritis which frequently complicates guinea pig scurvy is usually caused by it.

2. Variations in acquired immune bodies due to vitamin C deficiency

(*a*) *Results indicating that these immune bodies are altered.* When scorbutic guinea pigs were sensitized to horse serum, or red blood corpuscles, Zolog (16) found that they were much less sensitive to anaphylactic shock than normal diet controls. The minimum lethal dose was three to ten times higher in the animals with scurvy. Sereni (17), on the other hand, reported that scorbutic guinea pigs showed much more severe anaphylactic shock than the control animals. Hurwitz and Wessels (18) went further into the question and found that the uterine muscles of sensitized vitamin C deficient guinea pigs would not react either to the specific antigen or to smooth muscle stimulants, whereas the bronchial muscles of such animals reacted normally. In addition, when Bieling (5) immunized scorbutic guinea pigs with diphtheria toxin, he found that they did not produce as much antitoxin as the adequately fed controls.

(*b*) *Results indicating that these immune bodies are not reduced.* Scorbutic and normal guinea pigs produced agglutinins to B. typhosus equally well according to both Zilva (12) and Werkman (15). In addition, the former author stated that amboceptors to the same organism were also produced in normal amounts by guinea pigs on vitamin C deficient diets, and the same findings also held true for the rat. In 1922, Hess (19) reported that the diphtheria antitoxin production in scorbutic guinea pigs was as good as that in normal controls.

Summary of immunological investigations. I. Non-immune animals. In several of these studies conflicting results have been obtained. For example, Werkman reported that the opsonic indices of non-immune scorbutic guinea pigs were as high as those of normal animals, whereas Fortenato found them reduced. And again, Lawrynowicz stated that the presence or absence of scurvy did not affect the size of the Schick reaction in guinea pigs, whereas Bieling and also Arkwright found these reactions considerably reduced when scurvy was present. Other workers reported that tuberculin reactions were also considerably decreased. As the immunological significance of the Schick and tuberculin reactions are entirely different, one would infer that the general reactivity of scorbutic skin was depressed. The smaller Schick reactions were not due to any increased antitoxin in the animal, as Bieling

showed that these guinea pigs died more frequently and more quickly after the injection of large amounts of toxin. In fact, scorbutic guinea pigs seem more susceptible to the subcutaneous injections of toxic substances generally, e.g., to tuberculin, strychnine and poisonous fungus extract. Lawrynowicz suggests, on evidence gathered from the study of one animal only, that scurvy so lowers the resistance of a healthy carrier that it may become the prey of bacteria which formerly did not harm it. This sequence of events however might have occurred without the aid of the scurvy-producing diet. Leichentritt found that the substance in the blood which destroyed trypanosomes was reduced in scurvy, and further evidence of the reduced capacity of the scorbutic animal to cope with infections was provided by Dluzewski, who reported that the inflammatory reactions which followed the injection of foreign substances into the peritoneum were much reduced. Two authors stated that the complement titre was unchanged in scurvy, but a similar number of investigators found it increased. One of the latter however did not find it consistently raised, but at least it was never lowered.

II. Immune animals. Comparatively few studies have been carried out on such animals, and many of the results are conflicting.

For instance, Hess found that scorbutic guinea pigs could produce diphtheria antitoxin as well as normal animals, whereas Bieling states that this is not the case. Zilva and Werkman were not able to demonstrate any difference between the amounts of anti-typhoid antibodies produced by guinea pigs and rats lacking vitamin C and those fed adequate diets.

The results of the anaphylaxis experiments are of interest because most of them suggest a reduced activity in the tissues of animals suffering from scurvy, analogous to the lessened skin reactions.

3. Occurrence of spontaneous infections in vitamin C deficiency

(*a*) *Infections indicating a reduced resistance. I. Experimental.* In 1932, Suzuki (20) stated that the nasal mucous membrane and glands were atrophied and showed catarrhal inflammation in vitamin C deficient guinea pigs. The crushed oats, autoclaved milk diet that McCarrison (21) fed his guinea pigs is mainly lacking in vitamin C. He

found that the bladders in such animals at postmortem examination were tightly contracted and that the mucous membrane of this organ was congested and necrotic. The duodenum was also intensely congested and punched out ulcers were present in the intestines and sometimes in the stomach. Mackie and Chitre (22) gave their monkeys very small amounts of orange juice, but most of them developed scurvy, and in addition they showed in their large intestines very marked necrotic and ulcerated lesions, which were laden with common intestinal bacteria. These various pathological findings provide possible explanations for some of the frequent secondary infections that occur in cases of human scurvy.

In Höjer's (3) series only about 30 per cent of his severely scorbutic guinea pigs showed infections. This low figure may be partly explained by the fact that they survived for just a few weeks. On the other hand, 50 per cent of the animals with mild scurvy developed infectious lesions, and about 20 per cent of the much longer-lived normal animals showed similar lesions.

In the course of his experiments, Heymann (23) reported that he lost a large number of scorbutic guinea pigs with pneumococcic pneumonia.

II. Clinical—latent scurvy. Even before the onset of definite symptoms of human scurvy, in the so-called period of latent scurvy, the affected individual is particulaly susceptible to infections (24) and if these are contracted they run an unusually severe course.

In 1919, Wiltshire (25) described the occurrence of small conical swellings in the hair follicles of the legs of scorbutic Serbian troops and he also found them during the scurvy season (January and June) in apparently normal individuals. The latter were probably suffering from latent scurvy.

One of the most typical pathological lesions in scurvy is the increased permeability of the blood vessel wall which allows the blood to ooze into the tissues. Göthlin (26) was able to devise a method of measuring the permeability of the cutaneous capillaries. In 1931, he found that 18 per cent of a group of apparently healthy Swedish country school children (11 to 14 years) were suffering from vitamin C undernourishment. Hopkins (27) was able to associate a period of ill

health in boys in a preparatory school with a lack of fresh fruit and vegetables during the winter months. When a little fresh fruit was supplied, the minor ailments and the listlessness disappeared.

In children who are suffering from undiagnosed latent scurvy, vaccination may precipitate acute scorbutic symptoms (28, 29). Abels (29) quotes the case of an anemic, atrophic ten months old child who developed both scurvy and a high prolonged fever after vaccination. This may explain the reluctance of parents in backward regions of Austria towards having their children vaccinated in the winter, when no doubt their diets are partially deficient in this vitamin. In such children, coryza and pharyngitis may be surprisingly severe and may usher in evident scurvy, and skin ulcers and cystitis are also very prevalent. In fact, this author has gone so far as to say that manifest scurvy is always preceded by an infection. Other investigators (30) however have found this sequence of events to occur frequently, but not invariably. The increased metabolism caused by the infection probably accentuates the vitamin deficiency and hastens the appearance of active scurvy.

As in the case of the other deficiency diseases, there seems to be some predisposition to scurvy, as only a certain number of those on a uniformly deficient diet develop it (24b).

Manifest scurvy. Infections are very commonly associated with active scurvy (31), and Von Niedner (31) reported that scorbutic soldiers succumb to the slightest infection. Numerous authors (29, 32) have found respiratory infections, including grippe and pneumonia, to be very common in such individuals. One of these authors, Erdheim (33), stated that such diseases were frequently very grave and persistent in scorbutic children. Tuberculosis was also very prevalent in several series (32b, 34). In one of these, Salle and Rosenberg (34) found that all the deaths (17) in their 461 cases were from tuberculosis and that 9 to 22 per cent of their different groups of scorbutic patients suffered from this disease. They also remarked on the great frequency with which cases of infantile scurvy were complicated by florid tuberculosis. Diphtheria (8, 32b, 34b) and dysentery and typhoid (29, 34a, 35) were also very often encountered by various clinicians in scorbutic individuals. Mackie (22) described an epidemic of dysentery (Shiga) among scorbutic war refugees in the near East, which was almost as

virulent as cholera. Many investigators (32b, 35, 36) have reported that cystopyelitis and nephritis were very common, and that furuncles, paronychia and gun shot wounds (2, 32b, 35, 36) were often very difficult to clear up in scorbutic patients.

In 1927, Funk (37) stated that an epidemic of pneumonia in the Sudan disappeared when antiscorbutic treatment was given to the numerous cases of scurvy which appeared at about the same time. This would suggest that scurvy lowered the resistance to this infection.

Oral infections. If a guinea pig is kept on a completely vitamin C free diet for even two days, marked abnormalities are seen in its teeth (3, 30), and if such a diet is kept up for a few weeks, the teeth may become devitalized. Apical abscesses are prone to appear in such teeth later on. The same processes may occur in man (38), and the resistance to infection may be indirectly lowered by the presence of these bacterial foci. Höjer and Westin (30) also found that although enough vitamin C was given (1.2 minimum protective doses of orange juice) to prevent the appearance of any scorbutic changes in the teeth, except perhaps an uncertain hyperemia in the pulp cavity, the animals were still markedly susceptible to infection.

After analyzing the diets of groups of individuals, Hanke (39) stated that those whose diets were complete suffered from dental caries, gingival irritation or pyorrhoea much less frequently than those whose diets were deficient in either or both vitamin C and vitamin D. The details of the diets were unfortunately not given. Spongy gums, associated with infections, were cleared up by the use of an adequate diet plus 1 pint of orange juice, the juice of a lemon and from one-fourth to one-half a head of lettuce daily. The resistance to other infections, especially to colds, was raised at the same time, and in one individual a long standing osteo-myelitis was also cured. When pyorrhoea was present surgical measures had usually to be combined with the dietetic treatment unless the condition was very mild.

4. Susceptibility to artificially induced infections

(*a*) *Reduced resistance in vitamin C deficient animals.* In 1923, Findlay (40) reported that guinea pigs fed on a vimamin C deficient diet died more frequently after intraperitoneal injections of bacteria than

controls fed on normal diets. The organisms used were B. coli, staphylococcus aureus, streptococcus hemolyticus and pneumococcus.

In the same year, Werkman and his co-workers (15) found that there was a definitely, although not markedly, increased susceptibility to intraperitoneal injections of pneumococci or B. anthracis in scorbutic guinea pigs as compared with controls.

According to Abels (41), guinea pigs with scurvy die after intraperitoneal injection of B. coli, whereas normal animals withstand several times this dose.

B. aertrycke cultures were fed to 2 scorbutic and 2 normal guinea pigs by Grant (42). One of the scorbutic animals died and the three others were killed so that the spread of the bacilli to the various organs and the blood could be determined. Liver, spleen, lung and blood cultures were negative in the normal animals, whereas both the spleen and one of the blood and one of the liver cultures from the scorbutic animals yielded B. aertrycke. These findings would suggest that in scurvy the intestinal wall is more permeable to bacteria.

Schmidt-Weyland and Költzsch (43) infected normal and scorbutic guinea pigs by either inhalation or feeding, or by the combination of both methods, with a mixture of pneumococci and a fowl cholera pasteurella strain. They found that the animals on the scurvy producing diet were much more susceptible to such infections and that many of them died of pneumonia.

A trypanosome infection was set up in half their scorbutic guinea pigs by Nassau and Scherzer (44). They reported that this procedure hastened the onset of the scurvy, but only slightly decreased the duration of life.

Höjer (3) divided about ninety guinea pigs into several groups which were fed normal, completely vitamin C deficient, and several different partially C deficient diets. Half of each group was infected intramuscularly with probably too large a dose of a low virulent human strain of B. tuberculosis. All of the four severely scorbutic animals showed larger lesions than many of the rest. Only one guinea pig, which was fed the normal diet, showed no evidence of the disease, except for fibrous healing at the site of the subcutaneous injection. The course of the disease did not parallel the degree of scurvy in the partially scorbutic animals, but microscopic examination showed that

the connective tissue reaction to the tuberculous foci at a specified time after infection varied directly with the amount of vitamin C in the diet. The more vitamin C fed, the more adequate was the connective tissue response.

Coulard (45) stated that the tuberculous processes at the site of injection, the enlargement of the glands, and the lesions in the spleen developed much more rapidly in the scorbutic than in the normal guinea pig.

Guinea pigs suffering from slight scurvy were reported by Heymann (23) to be no more susceptible to tuberculosis than normal animals. When however the scurvy was moderately severe, marked loss in weight and early death (73 days) followed infection with a human strain of tuberculosis. Similarly infected guinea pigs fed on a normal diet lived 141 days on the average.

In order to induce intestinal tuberculosis in the guinea pig after the feeding of tuberculous sputum, McConkey (46) found that a partial deficiency of vitamins A, C and D was necessary. However, the lack of vitamin C seemed to be especially important.

Bieling (5) was able to produce a localized chronic tuberculosis in his guinea pigs. These animals were strong and well nourished and remained in such condition for over a year. If, however, they were put on a vitamin C free diet, they seemed particularly susceptible to scurvy and died long before the non-infected controls. These early deaths could be attributed to an activation of the chronic tuberculosis by the scurvy, although the sections showed neither very marked scurvy nor tuberculosis extensive or severe enough to explain the rapid deaths. This increased susceptibility of the tuberculous animal to scurvy was gradually built up, as recently infected animals did not react differently from uninfected ones. If the amount of vitamin C in the diet was reduced but not absent, the same phenomena were observed, but the onset of scurvy and the deaths were delayed. Apparently therefore the development of scurvy is accelerated when tuberculosis is present.

Quite a number of studies on this subject have been carried out by Mouriquand and his collaborators. In 1924, they (5b) showed that a larger percentage of scorbutic than of normal guinea pigs died after the injection of tuberculin. In 1925 (47), they determined the effect

of the injection of fairly large (10 million) and very small numbers (400) of tubercle bacilli into chronic scorbutic and normal guinea pigs. When the massive dose was used, for the first three weeks the deficient animals showed less extensive lesions and less loss in weight than the controls. After this time the scorbutic animals went rapidly down hill and died before the controls. With the smaller dose no initial refractory stage was seen, and the lesions in the animals with scurvy progressed more rapidly and led to earlier death. Two years later, they reported that if after feeding a diet completely deficient in vitamin C, a ration partially lacking in this factor was given, a chronic scurvy was established which was characterized by a tendency to relapses of the active scurvy, and by great susceptibility to infection with B. tuberculosis. When such an infection was set up, the animals suffering from chronic scurvy lost weight and died after a short time, and there was not the slightest evidence of tissue reaction against the bacilli, even though these were much attenuated. Normal animals similarly infected reacted with "multiple" sclerosis and lived considerably longer.

(*b*) *Increased resistance due to the addition of vitamin C.* The addition of vitamin C rich lemon juice to an adequate diet favorably influenced the course of tuberculosis in guinea pigs, according to Leichentritt (48). The experiments of Héricourt and Richet (49) may possibly be interpreted as providing further confirmation of the important rôle played by vitamin C in this disease. They found that if dogs were injected with raw meat juice they withstood a tuberculous infection better than similar animals injected with cooked meat juice. The cooking no doubt destroyed the vitamin C, but it may have had other deleterious effects on the meat juice as well. When the diet contained vitamin D, Grant (50) found that increasing the amount of vitamin C seemed to decrease the severity and extent of the tuberculous lesions in the lungs of guinea pigs.

(*c*) *No reduced resistance in vitamin C deficient animals.* In some of Grant's (50) other experiments she used diets in which the vitamins were unbalanced and the results were entirely different. For example, she reported that if vitamin D was deficient in the diet, the addition of vitamin C tended to increase the amount of tuberculosis in the

lungs, and the same effect also followed the substitution of vitamin C for vitamin D at the time of inoculation.

In one of their earlier publications (1922), Mouriquand (51) and his co-workers reported that chronic scurvy did not accelerate the course of tuberculosis in the guinea pig. Their later work gave results entirely opposed to those of this early investigation.

Bieling (5a) stated that "transitory milk or hunger scurvy" did not lead to a decreased resistance to infection.

When Jaffe (52) infected the leg bones, muscles or skin with staphylococci and put the guinea pigs on a scorbutogenic diet at the same time, he found that about half of them developed severe infections and that these animals lived longer (42 days) than the uninfected controls, and did not show scorbutic changes at death. If the infections were mild, death from scurvy occurred at about the usual time (21 to 30 days). If the animals were on the deficient diet for 10 days before infection, they died abnormally quickly from the scurvy (7 to 12 days). Baj (53) partially confirmed these findings when he reported that the characteristic bone changes of scurvy were less marked in animals infected with staphylococci. He suggested that antiscorbutic substances were formed by the bacteria. He also stated that the infections in scorbutic animals were no more severe than those in controls fed normal diets.

As many mice on a vitamin C deficient diet survived after intraperitoneal injections of mouse typhoid bacilli as mice on a complete diet, according to Hotta's (54) results.

Summary of artificial infection experiments. Relatively few of these investigators have brought forward evidence to the effect that a deficiency of vitamin C does not lead to a lower resistance to infection, and some criticism of their work is possible. For example, Hotta's results were based on one experiment including at the most 32 rats, and the rat is apparently able to synthesize this vitamin, and Mouriquand's numerous later results contradicted his earlier report, which need not therefore be considered further.

On the other hand, Findlay, Werkman and also Nassau found that a greater proportion of scorbutic than of normal guinea pigs died after intraperitoneal injections of bacteria or trypanosomes. The last two

authors stated that the reduction in the resistance was not marked. Jaffe infected the legs of guinea pigs that had been on a scurvy producing diet for ten days with staphylococci and found that they died very quickly. As Schmidt-Weyland's method of infection more nearly simulates that occurring in nature, it is probably preferable to those used by the above mentioned authors. Schmidt-Weyland's results showed many more deaths from pneumonia among the scorbutic animals.

The interest in the question of whether scurvy renders an animal particularly susceptible to tuberculosis was possibly engendered by clinical reports to that effect. The guinea pig develops scurvy readily and it is also very susceptible to tuberculosis. It is probably more susceptible to both these conditions than man. Consequently, in most of these experiments the resistance has had to be gauged either by variations in the duration of life or in the extent and nature of the lesions. As the course of tuberculosis in even normal guinea pigs is variable, these criteria are somewhat unsatisfactory. According to Heymann, the susceptibility varies with the severity of the scurvy. Slight scurvy does not affect the resistance, whereas animals suffering from moderately severe scurvy are less resistant and die quickly from tuberculosis. Höjer's experiments, which might have confirmed Heymann's, gave variable results from the point of view of duration of life. Coulard and also Mouriquand found that tuberculosis was fatal more quickly in scorbutic than in normal guinea pigs. When Höjer examined his animals in regard to the extent of the lesions, his results were more consistent, as the markedly scorbutic animals showed the greatest involvement, the normal the least, and in the slightly scorbutic the lesions were variable. Coulard also remarked on the more extensive tuberculosis found in scorbutic animals. Mouriquand noted that guinea pigs affected with chronic scurvy were unable to produce the usual connective tissue reaction to tubercle infection. Höjer also reported that the efficiency with which this reaction took place varied directly with the amount of vitamin C in the diet.

Several authors have provided information on the part played by bacteria in precipitating acute scurvy. Bieling found that animals with chronic tuberculosis were very susceptible to scurvy and Nassau also stated that the presence of a trypanosome infection seemed to

accelerate the onset of scurvy. Jaffe, on the other hand, found that a marked subcutaneous or osseous infection prevented the onset of scurvy and that a mild infection did not affect the course of this avitaminosis.

However, Jaffe's results may possibly have been due to the production of the vitamin by the bacteria. Baj, who suggested the above explanation, also found that the presence of a staphylococcic infection lessened the severity of the scurvy.

From Grant's experiment it would appear that the intestinal mucous membrane in animals suffering from scurvy is more permeable to bacteria, and McConkey indicates that the intestine in such animals is more susceptible to infection.

Three investigators also have shown that added amounts of vitamin C assist animals on normal diets in their reactions against tuberculosis.

5. The use of vitamin C in clinical infections

Numerous reports demonstrating the good effect of vitamin rich diets in clinical tuberculosis have been published, but it is impossible to decide what rôle vitamin C plays in such treatment. Also, one can not be sure that the good results which Höjer (3) obtained when he fed a series of twenty tuberculous children raw blood serum (50 to 100 cc.) daily for four months were due to the vitamin C contained in that substance. In a later experiment, the same author (30) compared the effect of the addition of vitamin C (one orange daily) or of added carbohydrate (a pastry) on sanitorium cases of tuberculosis. The patients were grouped in pairs as closely alike in age, sex, tuberculous involvement, and prognosis as possible. One of each pair received the orange and one the pastry. The sanitorium was in an isolated region where the supply of vegetables and fruit was limited, especially in the three months of the experiment (March, April and May). The highest mortality from this disease also usually occurred in these three months. Of the cases fed the extra vitamin C, 17 showed better, 3 showed similar, and 1 showed worse results than the controls. The cases were examined regularly by expert clinicians, and although the effects were not easy to evaluate, it appeared that the provision of plenty of vitamin C assisted in the healing of the tuberculous lesions. Woringer and Sala (55) advised generous additions of vitamin C to

whooping cough cases, for although scurvy is very rare in Strassburg, they saw four cases of whooping cough and scurvy together. McConkey (56) reported that the administration of cod liver oil and tomato juice has a favorable effect on intestinal tuberculosis which was secondary to a pulmonary infection. In order to determine whether the vitamin C was of value he gave three patients on normal diets a cod liver oil concentrate alone. No change could be seen until orange juice was added also, when two of them began to show satisfactory improvement. In a second test, he gave two cases irradiated brewer's yeast. Again they did not improve until the orange juice was administered also. The possibility that the good effects were due to the combination of the vitamins can not be ruled out, as none of the patients were given vitamin C alone. Bloch (57) is of the opinion that vitamin A is of more importance than vitamin C in the treatment of tuberculosis, but other authors (31) claim that generous amounts of vitamin C are essential in the treatment of such cases.

Summary. The results which have been published up to date suggest that this factor plays a very important rôle in the combatting of tuberculous infections, but further investigations will be necessary before this can be conclusively settled.

6. The mechanism underlying the decreased resistance in scurvy

According to Höjer (3), the decreased resistance in scurvy is due to the atrophy of the various organs in the body that protect it against infections. These organs include the lymph nodes, spleen and bone marrow. Findlay (40) had previously ascribed the low resistance which he found in scorbutic animals to the changes that were present in the bone marrow.

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VITAMIN E

In 1928, Blackberg (1) reported that rats lacking this vitamin were considerably more susceptible to tetanus toxin than the adequately fed controls. He also found that following the injection of typhoid bacilli the deficient animals did not produce agglutinins or bacteriolysins as well as the controls.

E reference

(1) See Ref. 6 under "Vitamin A and D."