

INFANTILE SCURVY

V. A STUDY OF ITS PATHOGENESIS *

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For some years we have been studying various aspects of the symptomatology and dietetics of infantile scurvy. In a recent paper¹ it was shown that pasteurized milk brings about this disorder in some cases unless an antiscorbutic food is included in the dietary. The type of scurvy induced under these conditions, as noted elsewhere, is not the textbook variety of this disease, but what has been termed latent or subacute scurvy, characterized by anemia and pallor, failure to gain in weight, rapidity of pulse and respiration, tenderness of the bones, and by a sharp recession of all these signs and symptoms when orange juice or other antiscorbutic foodstuff is given. In asserting that scurvy is brought about by pasteurized milk it should be emphasized that this is not synonymous with saying that this disorder is caused by heating the milk to the temperature of pasteurization. It is for this reason that we have, in this connection, referred to pasteurized milk rather than to pasteurization, as the former term includes not only the heating process, but the handling, subsequent cooling, aging and other factors.²

Some have questioned whether pasteurized milk is really involved in the production of scurvy. The fact, however, that when one gives a group of infants this food for a period of about six months, instances of scurvy occur, and that a cure is brought about when raw milk is substituted, taken in conjunction with the fact that if we feed the same number of infants on raw milk, cases of scurvy will not develop—these results- seem sufficient to warrant the deduction that pasteurized milk is a causative factor. The experience in Berlin, noted by Neumann³ and others, is most illuminating and convincing in this connection. In 1901 a large dairy in that city established a pasteurizing plant in which all milk was raised to a temperature of about 60 C. After an interval of some months infantile scurvy was reported from various sources throughout the city. Neumann³ writes about the situation as follows:

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1. Hess, A. F.: Jour. Am. Med. Assn., 1917, **68**, 239.

2. In the article¹ referred to above on "Subacute and Latent Infantile Scurvy" this point was brought out as follows: "In'referring to pasteurized milk as inducing scurvy I do not wish to state that the heating is necessarily altogether responsible for the result. There may .well be other contributory factors, such as the staleness of the milk."

3. Neumann, H.: Deutsch. Klin., 1904, **7**, 341.

"Whereas Heubner, Cassel and myself had seen only thirty-two cases of scurvy from 1896 to 1900, the number of cases suddenly rose from the year 1901, so that the same observers — not to mention a great many others — treated eighty-three cases in 1901 and 1902." An investigation was made as to the cause, and the pasteurization was discontinued. The result was that the number of cases decreased just as suddenly as they had increased. It should be added that the milk was also brought to the boiling point in the home, as is the custom throughout Germany.

For two years the milk which we used at the infant asylum was pasteurized commercially at 165 F. for thirty minutes; for two subsequent years the dealers raised it to a temperature of only 145 F. for thirty minutes. According to our experience, milk heated to the higher degree of temperature induces scurvy more readily than that which is brought to only 145, judging by the results of the four-year period. During the past year we have bought raw certified milk, the best milk which is sold in the city, and pasteurized it in the institution at 145 for thirty minutes. Various formulas were prepared with this milk, so that should any disorder develop we might be in a position to analyze the trouble and correct the dietary defect. Among six infants given milk which was pasteurized and prepared for feeding on the morning it was received, none developed scurvy. One infant in our institution which had been receiving commercially pasteurized milk for many months and which showed symptoms of subacute scurvy improved on this home pasteurized milk. It may be said, therefore, that this milk manifested almost no tendency to produce scurvy. How, then, did it differ from the commercially pasteurized milk which we had previously been buying? It differed mainly, as far as we can judge, in the interval which elapsed between the heating process and the consumption of the milk. In New York City the major portion of the bottled milk is Grade B, most of which is pasteurized after it reaches the city, soon after midnight; fully two-thirds of this milk is delivered to the consumer the same morning on which it is pasteurized; however, part of it is held over and delivered twenty-four hours later. The better milk, Grade A, is largely pasteurized in the country, so that an interval of twenty-four hours elapses between the heating and delivery.⁴ In order to reproduce these conditions, we held over some of the pasteurized milk for twenty-four hours on ice, so that it corresponded more closely to Grade A milk. Of eight infants who received formulas made with

4. We found that as a matter of fact the interval following pasteurization was forty-eight hours in milk which we received and which had been pasteurized at the creamery. The milk was stored by the dealers for twenty-four hours in the city, so as to provide a constant supply in case of delay or failure of delivery from the country.

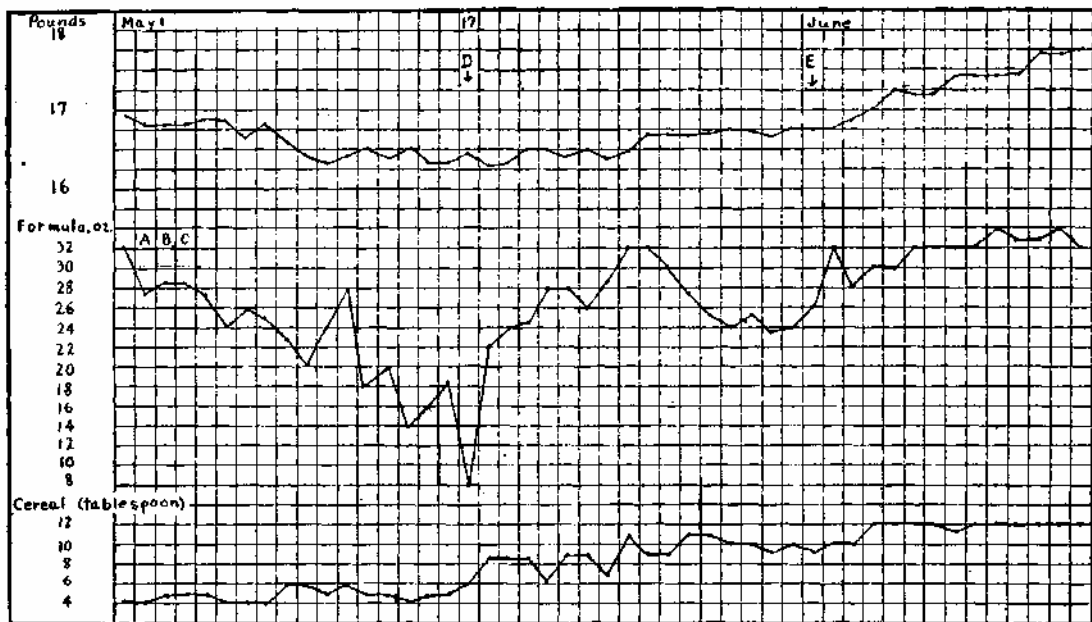
this type of milk (Pasteurized II) two showed scorbutic signs which promptly yielded to orange juice. In one of them the onset seemed to have been precipitated by an intercurrent infection of "grippe." Although these results point to the influence of the freshness or staleness of pasteurized milk, they likewise indicate that aging must be considered only a mild scorbutic agent. This deduction is forced on us by the mild nature of the scorbutic process, by the paucity of cases developing, and by the further observation that among eight other infants who were given the milk which had been kept on the ice for forty-eight hours following pasteurization (Pasteurized III), only two evinced symptoms of subacute scurvy. That aging affects raw milk similarly was shown by the fact that one baby developed latent scurvy among a group of four who were receiving Raw III milk, that is, certified milk which was kept for forty-eight hours on the ice before preparing the formula. This infant developed an eczematous skin condition, to which we have drawn attention before, and which we have frequently noted in association with scurvy. When orange juice was given the skin lesions disappeared, the general condition improved, and there was a marked gain in weight.

That the degree of heat to which the milk is subjected is not an all important factor in rendering the dietary unsuitable was clearly shown in the cases of some infants that received milk which had been boiled for a period of five minutes. After an interval of five months one well nourished infant, 11 months of age and weighing 18% pounds, showed pallor, some periosteal tenderness, slight peridental hemorrhage and a rapid pulse. These symptoms were alleviated by a substitution of raw milk. It is furthermore evident from the reports of others that boiled milk cannot be an important etiologic factor in bringing about a scorbutic condition. When we consider the thousands of infants that receive milk of this kind and thrive, and that a moderate number must be deprived of orange juice or other antiscorbutic food, we must realize that boiled milk can lead to scurvy only in a mild degree. Statistics such as those of Variot,⁵ who has distributed in his outpatient department during a period of twelve years 400,000 quarts of sterilized milk (heated in the half liter bottles and hermetically sealed at the farm) without observing a case of scurvy, must be accorded weight in this connection. It is to be noted, however, that Variot remarks that these infants frequently develop anemia unless additional diet is given, so that it must be considered open to question whether careful and repeated examinations (such as can be carried out only at home or in an institution) might not have uncovered some of the minor manifestations of scurvy. Of course, unless it is certain

5. Variot, G.: *Compt. rend, de l'Acad. d. sc.*, 1905, **139**, 1002.

that these infants were receiving only sterilized milk, and absolutely no other food, for a period of at least six months, they cannot be considered as affording a test of the question.

Four infants were given the milk for forty-eight hours after it had been boiled, and in one instance inconclusive signs of scurvy developed. That aging, however, may also play a role in relation to the use of sterilized milk is well illustrated by some cases in the literature where babies developed scurvy on sterilized milk which had been sent to the country, and where they recovered on receiving the same milk freshly sterilized. In some of these instances the milk was some weeks old. There is a point, one which is lost sight of, which should be emphasized



Joseph G., aged 9 months. Chart showing stationary weight in spite of marked variation of fluid intake (due to oliguria followed by diuresis). A = Schloss milk; B = cod liver oil; C = egg yolk; D = 1 ounce of orange juice; E = potato (orange juice stopped).

in connection with a discussion of the role of heated milk in the causation of scurvy. It is taken for granted that if pasteurization will induce scurvy, heating the milk to a still higher degree will certainly lead to this more surely and constantly. This deduction is by no means warranted. Indeed, from personal experience, it would seem that *milk which has been boiled is less apt to induce scurvy than milk which has been pasteurised*, heated to 165 or a lower temperature. This was well illustrated by putting four infants, who were receiving freshly pasteurized milk, on "evaporated milk," so-called because in the course of heating for five to six hours it had been reduced to one-quarter its volume. It thus resembled in many respects the evaporated milk to be bought in the market. In preparing the formulas for these infants

due cognizance was taken of the concentration of fat, sugar and proteins of the milk. This food was well taken by the babies, and after a period of five months none manifested signs of scurvy.

As it has been claimed that scurvy is an acidosis, brought about by a long continued diet of high acidity, the reaction of the various diets was recorded. This is given in Table 1. It will be seen that pasteurized milk does not increase in acidity during the first twenty-four hours, and but little after forty-eight hours. Schloss milk, which is very prone to induce scurvy, has a very low acidity. Evidently the answer does not lie in this direction. It is probable that pasteurized milk

TABLE 1.—ACIDITY OF THE VARIOUS MILK PREPARATIONS USED

Type of Milk	Age, Hours	Number of Cubic Centimeters of Tenth-Normal Sodium Hydroxid Required to Neutralize 100 C.c. Milk							
		April 13	April 14	April 16	April 17	April 18	April 19	April 20	April 21
Raw.....	Fresh	14.9	14.1	16.9	18	18	17	17	18
Sterilized.....	Fresh	15.1	14.2	16.3	16	16	19	18	19
Sterilized (III).....	48	16.0	16.4	16.5	23	21	21	23	20
Pasteurized (I).....	Fresh	17.3	15.3	17.9	18	18	19	16	18
Pasteurized (II).....	24	17.5	15.7	17.3	17	17	18	18	20
Pasteurized (III).....	48	20.1	17.3	17.7	19	20	20	18	22
Pasteurized (III).....	72*	16.6	23.2	17.0	18	27	19	21	24
Pasteurized (II) with flour.....	24	13	13	14	16
Pasteurized (III) with flour.....	48	13	36	14	19	16
Evaporated milk.....	24	29	21	21
Schloss milk.....	Fresh	8.4	6.4	8.7	6	7	7	6	12
Albumin milk.....	Fresh	26.4	28.6	41.4	40	46	34	39	49

* Last bottle of pasteurized III formula given on the following morning.

† Formula of two-thirds milk, one-third barley water, with 3 per cent. cane sugar.

constitutes quite a different medium for the growth of bacteria than raw milk, and that it may favor the development of gas-forming or other types of bacteria.

In view of the fact that it has been stated by Braddon and Cooper¹ in connection with beriberi, that there is a definite relationship between the amount of carbohydrate in the diet and the occurrence of this disorder, for example, that when the carbohydrate is doubled, the rate of onset of beriberi is increased proportionately, it seemed worth while to observe whether this relationship obtained for scurvy. Accordingly, 3 per cent, of flour was added to the diet of four infants which were

6. Braddon, W. L., and Cooper, E. A.: Brit. Med. Jour., June 20, 1915.

receiving the usual mixture of freshly pasteurized milk and barley water. In this way a milk food was prepared similar to some of the commonly used proprietary foods.⁷ No noticeable effect was observed—certainly no result which could be interpreted as indicating the existence of a biologic law such as Braddon and Cooper have formulated for beriberi, which presupposes that carbohydrate requires a proportionate amount of "vitamin" for its metabolism in the body. On the other hand, the proprietary foods, composed of carbohydrates, which are stale and have been subjected to a high degree of heat, do seem to lead to scurvy.

From the foregoing it would seem clear that the preparation and condition of the milk may lead to the development of infantile scurvy. It is equally evident, however, that the milk cannot be the sole or determining etiologic factor. The mere fact that only a few of the infants developed signs of this disorder under the various dietaries is convincing evidence of the participation of one or more additional causative agents. There is, indeed, no dietary of which it can be stated that it is certain to produce scurvy, no single food preparation of which we can postulate that, provided it is taken for a sufficiently long period of time, scurvy will certainly manifest itself. The nearest approach to this situation occurs when Keller's "malt soup" is fed to infants. It can be confidently stated that if infants are fed with this mixture of malt, flour, milk, potassium carbonate and water for five to six months, especially if pasteurized milk is used, the majority will evince definite signs of scurvy. Greatly to our surprise, we experienced this result a few years ago while we were using pasteurized milk. The fact that the disorder comes about more readily when pasteurized milk is employed, gives weight to the opinion of Neumann that the heating of milk for a second time lends it scorbutic qualities. We wish, however, to qualify his statement by adding that this seems, to be true only if there is an interval between the two heating processes. If one pasteurizes the milk, allows it to cool, and then immediately brings it to the boiling point, the twofold heating does not produce the same deleterious effect.

As is well known, scurvy, infantile scurvy, beriberi, pellagra, rickets, and some other diseases have been linked together into one group; it is evident that there are symptomatic and pathologic similarities among these diseases sufficient to render it profitable to group them together. In recent papers we have drawn attention to common symptoms in infantile scurvy and beriberi, such as cardiac enlargement and tachycardia, and others have brought out points of resemblance between

7. The flour was cooked with the barley water and sugar and added to the pasteurized milk.

members of this group. The basis of the classification, however, is etiologic rather than symptomatic, and is founded on the assumption that they all are nutritional or rather dietary diseases. Although there has been an increasing tendency to admit their similarity and even their dietary nature, two totally different conceptions of their pathogenesis are current. One school regards them purely as "deficiency diseases," whereas the other believes that they are of toxic origin. Some twenty years ago Eijkmann,⁸ in a paper which has become classic, described a polyneuritis which he was able to produce in fowl and which closely resembled the beriberi of man. He attributed this disorder to a toxin found in the intestinal canal, and many subsequent investigators, repeating or enlarging on his experiments, expressed themselves of the same mind. Kohlbruegge⁹ was the first, however, to suggest a grouping of these diseases, designating them by the name of "fermentative diseases" and asserting that they were due to poisons which were formed by harmful bacteria which had gained predominance in the intestinal canal. Very recently Williams,¹⁰ after many years of work in this field, has also come to the conclusion that this group of diseases is of toxic origin. On the other hand, an entirely different conception has been in vogue for the past few years, mainly due to the writings of Funk.¹¹ This conceives of these disorders as being due entirely to a lack of essential food substances, the "vitamins"— as being essentially deficiency diseases. A division of opinion similar to that which exists regarding the etiology of this entire group of diseases, and as to beriberi in particular, exists in regard to the pathogenesis of infantile scurvy. Barlow took the point of view that it was brought about by a diet which had been deprived of some of its essential constituents. The excellent report of the American Pediatric Society¹² cautiously refrained from expressing a decided opinion on this point, merely declaring that "the development of the disease follows in each case the prolonged employment of some diet, unsuitable to the individual child." An interesting minority report of this committee signed by Caille, however, rendered the opinion that it is "a chronic ptomain poisoning due to the absorption of toxins." Neumann,³ one of the most thoughtful observers and students of infantile scurvy, also regarded it as "a chronic poisoning." Hart,¹³ who drew his conclusions mainly from experiments on monkeys, characterizes it as a "dyspeptic intoxication." Nevertheless, the literature contains many articles which accept Funk's

8. Eijkmann, C.: *Virchows Arch. f. path. Anat.*, 1897, p. 253.

9. Kohlbruegge, J.: *Centralbl. f. Bakteriol., Orig.*, 1911, **60**, 223.

10. Williams, R. R.: *Am. Med.*, November, 1916, p. 756.

11. Funk, C.: *Die Vitamine*. J. F. Bergmann, Wiesbaden, 1914.

12. *Rep. Am. Pediatric Soc.: Arch. Pediat.*, July, 1898, p. 481.

13. Hart, C.: *Jahrb. f. Kinderh.*, 1912, **76**, 507.

point of view in its entirety and agree that we are dealing with a pure "deficiency disease."

A feature which has forced itself on the attention of many who have written on the subject is the multiplicity and variety of the foods which may bring about scurvy in the infant. Pasteurized milk, milk containing a high fat percentage, buttermilk containing but little fat, albumin milk containing much protein, and the proprietary foods rich in starches, are among the varied and incongruous number. It is of course possible that these dietaries, however different they may seem, may all be lacking a common chemical constituent. What tends strongly against this point of view is the fact, already mentioned, that with none of these dietaries can scurvy be brought about with regularity. This lack of reaction between cause and effect must lead us to conclude that the deficiency cannot be the sole cause; indeed, that it does not act directly in bringing about the disorder.

In order to gain a clearer idea as to the possible nature of the etiologic factors it will be well to turn back and consider the nature of the symptoms and pathologic changes of infantile scurvy. In the first place it should be remembered that we have signs of nerve involvement. These comprise cardiorespiratory phenomena, clearly indicating involvement of the pneumogastric nerves, occasionally changes visible in the optic disks, abnormalities of the deep reflexes, and probably sensory disturbances. The symptoms and changes common to this group of diseases, therefore, resemble those brought about by poisons of various kinds — the cottonseed poisoning in swine,¹⁴ the toxic products of the wheat embryo,¹⁵ or even mineral poisons such as mercurial poisoning in man.¹⁶ The nervous symptoms, especially the irritability of the heart, may be compared to those of the enterogenous intoxication or enterotoxic polyneuritis described by Von Noorden.¹⁷ The experiments of Abderhalden and Lampe¹⁸ lend weight to the view of the formation of a toxin in the intestinal tract in this disorder. These investigators were able to bring about polyneuritis in pigeons and hogs by means of a restricted diet, and to cure the animals promptly by means of catharsis, castor oil or magnesium sulphate.

14. Rommel and Vedder, E.: Jour. Agric. Research, 1915, **5**, 489.

15. Hart, E. B., and McCollum, E. V.: Jour. Biol. Chem., 1914, **19**, 373.

16. In chronic mercurial poisoning the following suggestive symptoms occur: anemia, bleeding and spongy gums, loosening of the teeth, a quickened pulse, ulcers of the extremities. At times mercury attacks the nervous system, producing palsy. The resemblance is heightened by the fact that calcium metastases have been found in the muscles—in experimental scurvy (Hart) comparable to those characteristic of mercurial poisoning.

17. Von Noorden, C.: Berl. klin. Wchnschr., 1913, **50**, 51.

18. Abderhalden, E., and Lampe, A. E.: Ztschr. f. d. ges. Exper. Med., 1913, **1**, 296.

They were led to attempt a cure by this means as they had noted that the polyneuritic pigeons passed very little stool and that the intestines at necropsy were markedly overfilled. They concluded that, particularly in the pig, toxic products are formed in the intestine. These novel experiments gain additional interest in view of similar results reported by McCollum¹⁹ in connection with the scurvy of guinea-pigs. It may be inquired as to the condition of intestines in infantile scurvy. When we search the necropsy protocols for lesions of the intestinal tract we find that in most cases there are merely occasional hemorrhages and swelling of the follicles and of the neighboring mesenteric glands. In some cases there is inflammation or ulceration of the colon.²⁰ If a toxin is to be regarded as the proximate cause of infantile scurvy, the question naturally arises as to the nature of the toxin.¹ Is it exogenous or endogenous? There are some sound reasons for believing that the poison generally is not introduced preformed in the food. In the first place, infantile scurvy frequently develops in babies who are given milk of the very best grade; indeed, in contradistinction to rickets, it is not preeminently a disease of the poor. Furthermore, there is no relation between the concentration of the food mixture and its liability to induce scurvy. If, among a large number of infants receiving pasteurized milk from a common source, some are given milk diluted by one-half, others given it diluted by one-third, and still others whole milk, the last group will not show a preponderating tendency to scurvy, as we should expect were the poison contained in the food. Nor is it at all uncommon to encounter scurvy in an infant which has been fed with a very dilute milk mixture. The other side of this question, however, cannot be entirely dismissed. We should bear in mind that stale pasteurized milk is more apt to produce scurvy than freshly pasteurized, a fact which might be interpreted as in favor of an exogenous toxin. Again, the reports of the scurvy of adults being occasioned by decomposed food, as in Nansen's polar expedition and as

19. McCollum, E. V.: *Jour. Am. Med. Assn.*, 1917, **68**, 1381.

20. There is one lesion in the intestinal tract to which we would call attention, as it was present in a necropsy performed a few years ago and has been recorded by others—a marked injection of the mucous membrane of the first part of the duodenum. Additional significance would seem to be attached to this lesion in view of the fact that it is noted in some necropsy protocols in cases of beriberi and of pellagra. It may well be that this inflammation is the result of products excreted by the liver and poured into the intestine at this point.

21. There are probably many factors which influence the occurrence of scurvy. Certainly climate plays a role. We have frequently found that scorbutic symptoms will disappear when infants are placed out of doors and exposed to the sun and air in the spring months. Scurvy is more prevalent in the winter, as is rickets. No doubt general nutritional diseases act as predisposing factors, among which rickets and syphilis are important.

reported on ships so frequently in the past, cannot be disregarded, and seem open to the interpretation as due, in part at least, to food poisoning. The experiments of Jackson and Harley,²² who produced scurvy in monkeys by feeding them with tainted tinned meat, would seem to fortify this interpretation. But, as we have said, infantile scurvy develops in the overwhelming majority of cases on food which is not decomposed, so that, although we acknowledge the occasional role of exogenous poisons, we believe that the toxin is usually elaborated within the human body. As is well known, toxins are continually being formed in the intestinal canal by bacterial growth. We are protected from the deleterious action partly by the counteraction of neutralizing bacteria. Should this protective force fail, the toxins may gain access to the tissues of the body. This is what happens in infantile scurvy. Whether the toxins differ in kind from those normally present in the intestine, or whether they are always the same, it is impossible to say. The various types of scurvy, as well as of rickets and of beriberi, may be due to differences in this regard.

According to this mew, infantile scurvy is essentially a scorbutic auto-intoxication or intestinal intoxication; the diet is faulty in not-being capable of inhibiting the elaboration of the poison. This raises the question, which must be left open for discussion, as to whether, from an etiologic point of view, infantile scurvy should be regarded as an entity, or whether its symptoms cannot be produced by various poisons, some exogenous" and others endogenous, formed as the result of an unbalanced flora in the intestinal canal.

If we consider scurvy an intestinal intoxication, we naturally inquire as to the functioning of the bowels in this disorder. This has been frequently discussed by writers on this subject, but a consensus of opinion is not apparent. Of the cases reported by the American Pediatric Society the bowels were regular in seventy-four instances, irregular in fifteen, constipated in 126, and diarrheal in seventy-seven. This question has assumed additional interest in view of recent experimental work on animals. As has been stated, Abderhalden and Lampe,¹⁸ as well as McCollum,¹⁹ found marked constipation in the course of their experiments. The latter expressed his conclusions in these words: "Scurvy in guinea-pigs is the result of retention of feces. I do not know whether or not the same is true of human scurvy."

Of course, there can be no question as to whether retention of feces by itself can bring about scurvy in infants; this is excluded by the marked instances of constipation frequently encountered among thriving babies. The majority of bottle fed babies and a large number

22. Jackson, F. G., and Harley, V.: Lancet, London, 1900, p. 1184.

of the breast fed suffer from a greater or less degree of constipation. On looking up our-records of infantile scurvy from this point of view, and comparing them with nonscorbutic infants, we have not been able to note a characteristic distinction. Some of the infants which developed scurvy had normal stools as far as gross examination disclosed, others suffered from constipation, while a greater number showed a record of occasional loose stools. In reviewing the cases reported by others it would seem that, as in the report of the American Pediatric Society, this same lack of uniformity is manifest, but that in the advanced cases the stools are more often diarrheal. In this connection we must bear in mind that the malt soup preparation, the diet which, in our-experience, has been associated with scurvy most frequently, is essentially laxative and almost never induces constipation. And, on the other hand, the most potent antiscorbutic both for adults and for infants, one which is effective at times when fruit juices have proved unavailing, is potato, a food which has no distinct laxative properties. It may be added, as noted elsewhere, that scurvy was found to develop in infants in spite of their receiving cod liver oil or olive oil for long periods. We do not wish to conclude that the retention of feces is a negligible factor in the scurvy of infants, but rather that its role is quite secondary. When we assume that a poison is contained in the intestinal canal, it is evident that catharsis will be of value, and that constipation will aid in its absorption. This is true of all poisoning which occurs by way of the alimentary canal; for example, in lead poisoning, where catharsis has always been granted a distinct therapeutic place. It is probable that marked constipation may be assigned as one of the causes for the frequent occurrence of scurvy and allied intestinal intoxications among the insane, who neglect their bodily functions.

We have said that the value of potato cannot be ascribed to laxative properties. The same is true of orange juice, which is very mildly laxative, and cannot be depended on to relieve constipation in infants. Its therapeutic value in scurvy is probably due to its influence on the flora of the intestine and to its diuretic effect.

It is surprising that attention has not been called to the fact that *there is a diminished excretion of urine in infantile scurvy*. We have frequently observed this phenomenon, and its occurrence has been noted by the nurses. This oliguria is interesting from several points of view. It accounts in part for the edema which is so frequently met with in this disorder, and is of especial interest in connection with the relation of body weight to infantile scurvy. Before noting this disturbance of metabolism we were at a loss to interpret the paradoxical phenomena of a scorbutic infant which was given orange juice

being greatly improved and consuming considerable more food, but nevertheless failing to gain, or even reacting with a loss of weight. It was only when it was noted that the orange juice brought about a sudden outpouring of urine that the explanation was evident. Whereas before orange juice was given a baby urinated but three or four times a day, passing but 4 to 6 ounces of urine, thereafter it urinated fifteen to twenty times a day and passed 20 to 30 ounces of urine. A chart illustrating this condition is appended. It is probable that the citric acid of the orange juice induces the diuretic action. We had at various times tested the curative value of citric acid, considered by Netter²³ to be the essential deficiency of infantile scurvy, but, although we were able to bring about diuresis and to alleviate the symptoms temporarily, we were never able to effect a complete or permanent cure. In this connection we wish to call attention to the fact, mentioned also by Abderhalden and Lampe, that Funk's vitamins are claimed to belong to the pyridin and pyrimidin groups, which possess diuretic properties. It is probable that the kidneys play a considerable role in infantile scurvy, its clinical course depending to some extent on the activity of their function, and that toxins are eliminated at an early stage by this route. This statement seems warranted in view of the frequency of urinary symptoms in scurvy — casts and blood cells in the urine, and the signs of parenchymatous inflammation which the kidneys may show at necropsy.²⁴

Renewed interest has been awakened in the study of scurvy since it has become possible to reproduce the disease in animals. The first experimental work of this kind is generally associated with the names of Hoist²⁵ and his co-workers, who induced scurvy in guinea-pigs by means of a diet of cereal grains. It should be noted, however, that the same result had been accomplished some years previously in this country by Theobald Smith.²⁶ During the past few years Baumann and Howard²⁷ have carried out the first metabolism investigations on scorbutic guinea-pigs. Although this work on animals has increased our knowledge considerably and is certain to open new paths of investigation, caution should be exercised in transferring the results to human beings. The fact that we are able to produce scurvy in guinea-

23. Netter, M.: *Bull. Soc. pediat., Paris*, 1902, **4**, 298.

24. Pinner, F.: *Deutsch. med. Wchnschr.*, 1896, **22**, 546.

25. Hoist, H., and Froelich, D.: *Ztschr. f. Hyg. u. Infektionskr.*, 1912, 72.

26. In a bulletin on "Bacilli in Swine Disease," published by the Bureau of Animal Industry, 1895-1896, Theobald Smith says (p. 172): "When guinea-pigs are fed with cereals (it has been observed for some years in this laboratory), with bran and oats mixed, without any grass, clover or succulent vegetables, such as cabbage, a peculiar disease, chiefly recognizable by subcutaneous extravasation of blood, carries them off in from four to eight weeks."

27. Baumann, L., and Howard, C. P.: *Am. Jour. Med. Sc.*, 1917, **153**, 650.

pigs by means of raw milk, a diet which effects a cure in infants, is evidence that some of the underlying conditions are different. An elaborate investigation on guinea-pig scurvy has recently appeared comprising papers by Jackson and Moody²⁸ and Jackson and Moore,²⁹ one entitled "Studies on Experimental Scurvy in Guinea-Pigs," the other "Bacteriologic Studies on Experimental Scurvy in Guinea-Pigs." The latter article is of especial interest, as it suggests tentatively that scurvy may be a bacterial infection. These investigators cultivated a diplococcus from the tissues of scorbutic animals after death, reproduced hemorrhages by inoculating cultures of these micro-organisms into the circulation, and recovered the bacteria from the tissues some weeks later. This conception of scurvy as an infectious disease has been brought forward from time to time, especially in relation to epidemics of adult scurvy. Some years ago Ausset³⁰ claimed to have isolated "a pasteurilla type of organism" from a case of infantile scurvy, and suggested that it was the causative agent of this disease. On the other hand, Hart,³¹ Rehn,³² Hirschsprung,³³ von Starck,³⁴ and Schmorl³⁵ have failed to find bacteria in the blood, although the total number of cultures seems to have been small. Czerny³⁶ reports negative growth from fluid aspirated from affected joints. Jackson and Moody's results, while most interesting, are open to the criticism that bacteria were found only after death, and that all blood cultures proved negative. This is, as stated, the same experience as has been encountered in infants.

One of the most striking clinical phenomena of infantile scurvy is the marked susceptibility to infection which it entails — the frequent attacks of "grippe," the widespread occurrence of nasal diphtheria, the furunculosis of the skin, the danger of pneumonia in advanced cases. Whether this is to be in part attributed to the disturbance in water metabolism, in view of the fact that a similar susceptibility exists in *Mehlnärschaden* cases, where the tissues likewise contain an excess of water, there is no basis for judging, but the clinical fact is striking and significant.

It is as one of these secondary infections, we believe, that the findings in the guinea-pigs are to be interpreted. In this connection it is

28. Jackson, L., and Moody, A. M.: Jour. Infect. Dis., 1916, **19**, 478.

29. Jackson, L., and Moore, J. J.: Jour. Infect. Dis., 1916, **19**, 511.

30. Ausset, E.: Bull. Soc. pediat, Paris, 1902, 4.

31. Hart, C.: Jahrb. f. Kinderh., 1912, **76**, 506.

32. Rehn: Med. Klin., 1907, No. 30, p. 892.

33. Hirschsprung, H.: Jahrb. f. Kinderh., 1896, **41**, 1.

34. von Starck, W.: Handbuch d. Kinderh., Pfaundler and Schlossmann, 1906.

35. Schmorl: Jahrb. f. Kinderh., 1907, **65**.

36. Czerny, A., and Keller, A.: Des Kindes Ernährung, Ernährungstorungen, Leipzig, 1907, **2**, Ch. 6.

well once more to emphasize that when we refer to scurvy we do not regard it as a disease characterized by hemorrhages, but as a nutritional disorder which exists for months before the subperiosteal or other hemorrhages develop. This nutritional disorder, this simple scurvy, is not attributable to a bacterial invasion, although it leads to and is responsible for its occurrence. From the same point of view orange juice and other antiscorbutics are to be considered as of prime value in combating the toxic nutritional disturbance, but of no direct value in doing away with those hemorrhages which are brought about by bacterial infection. A hemorrhage of infectious origin, in contradistinction to those of toxic origin, must be regarded simply as a focal complication. The clinical course of many of these effusions, receding spontaneously or developing as the scorbutic condition improves, shows that they have local and not general significance. It is highly important that blood cultures should be carried out in the course of scurvy, and that particular attention should be paid to the stage of the disorder in which they are made.

Scurvy sometimes occurs in epidemic form. A few years ago we had the opportunity of observing an epidemic of infantile scurvy in connection with an outbreak of "grippe" at the infant asylum. We do not suggest this as a distinct type of this disease, for, as we have just said, infection is common as a secondary stage of scurvy. At times, however, when infection is widespread and scorbutic malnutrition exists among a group of infants, a considerable number of them may become infected and develop a hemorrhagic form of scurvy. It is an outbreak of this kind which we wish to describe in detail.

In February twelve infants in one ward developed fever and soon showed symptoms of various infections: otitis, pneumonia, nephritis, adenitis, etc. Three died of pneumonia; of the nine who recovered, seven suffered from what we shall term infectious scurvy, meaning by this a type of the disorder brought about by superimposing a secondary infection on the primary nutritional disturbance. Some of the infants showed signs of alimentary intoxication; most of them had no fever at the time the hemorrhages occurred, although they may have had a rise of temperature when the infection began. In April a second epidemic of "grippe" took place and three more infants developed scurvy. The signs were mainly hemorrhagic, developing at sites both atypical and typical for scurvy. They occurred as follows: Case 1, left diaphysis of humerus and tibia; face; anterior abdominal wall at site of serum injection; right eyelid; Case 2, abdominal wall; cranium; vertebral column; external ear; Case 3, diaphysis of left femur; Case 4, cranial bones and external ear; Case 5, external ear and face; Case 6, diaphysis of tibia; Case 7, abdomen (Table 2).

These infants were receiving formulas made from milk pasteurized at 160 F. for twenty minutes.

It is striking that many of the hemorrhagic signs above outlined are quite different from those encountered in infantile scurvy. We have never met with such widespread subcutaneous hemorrhages, and have noted them in the literature only in the most advanced cases. But what makes these cases stand out sharply from ordinary scurvy is not

TABLE 2.—DATA OF EPIDEMIC OF SCURVY

Case	Age, Mos.	Weight		Site of Hemorrhages	Date	Diet	Remarks
		Lbs.	Oz.				
1 J. H.	6½	9	6	Humerus, tibia, face	Apr. 19	Breast milk (1 week); breast milk, buttermilk and orange juice	Grippe since end of February; nephri- tis; v. Pirquet neg- ative
		10	4	Upper eyelid.....	May 9		
2. L. S.	5	12	14	External ear, parietal bones, vertebral column, abdominal wall	May 4	Pasteurized milk formula; orange juice 1 oz. daily since April 22	Twitchings and convulsions; signs of intoxication; red blood cells in urine; fever to 101 F.; v. Pirquet negative
3. A. R.	10	12	8	Femur.....	Apr. 19	Pasteurized milk formula; vegetables for a month; orange juice longer; getting orange juice and vegetables	Grippe end of January; again in April; fever until April 17; v. Pirquet positive; gums negative
				Femur again swollen and tender	June 4		
4. D. E.	5	7		Both ears; parietal bones	Apr. 29	Breast milk since April 19; May 30, changed to pasteurized milk	Grippe throughout March; intoxication; nephritis; no relapse although no orange juice given
5. T. K.	10	15	13	Ear and face.....	Apr. 27	Pasteurized milk, cereal, vegetable, soup; orange juice since April 15	Two teeth; gums negative; v. Pirquet negative
6. P. G.	4	8	4	Tibia.....	May 8	Pasteurized milk formula	Grippe end of February and first half of March; gained 20 oz. during last month; v. Pirquet negative
7. I. P.	2	6	4	Abdomen.....	Mar. 7	Breast milk for past week	Grippe; probable source of epidemic

so much their exceptional symptomatology as their lack of response to specific therapy. Two had received breast milk for two weeks previous to the onset of symptoms; one an ounce of orange juice for two weeks; one an ounce of orange juice and also vegetable for two months previously; one vegetable and orange for a week; and another vegetable for an indefinite period before the onset. One baby, 9 months old, which had a tender swelling of the diaphysis of the femur in April, had a relapse of symptoms in June in spite of having received

orange juice and vegetables throughout the intervening period. It should be noted that of the seven infants four were under 6 months of age, which, from a practical standpoint, and although subject to exceptions, is rightly regarded as the minimum age for the hemorrhagic stage of this disorder. Again, although two babies had teeth, neither showed spongy gums nor peridental hemorrhage. The swellings of the long bones, however, were quite typical of the subperiosteal hemorrhages of infantile scurvy, and are open to no other clinical diagnosis.

How are we to interpret this picture? The ages of the infants, the distribution of the hemorrhages, the development of signs in some cases in spite of antiscorbutic diet, the sharply defined epidemic character of the disease, distinguish it from the scurvy we commonly meet with. We believe that the epidemic was brought about by a bacterial invasion. Whereas usually scorbutic intoxication must be prolonged for a period of about six months to allow the secondary invasion of bacteria, in this instance, due probably to the peculiar nature of the bacteria, invasion occurred early and in some infants which were receiving an antiscorbutic diet. In most of these instances, however, it should be noted that the infants had been receiving pasteurized milk for months, and the antiscorbutic foodstuff had been added but a few weeks previously. Latent scurvy was prematurely changed to florid scurvy by the presence of a ward infection; an epidemic of "grippe" precipitated an epidemic of scurvy exceptional in its hemorrhagic tendency.

In closing we may add that this epidemic resembles the epidemics of melena neonatorum which occur from time to time in lying-in hospitals and which formerly visited these institutions so frequently. Not long ago we had the opportunity of observing an epidemic of this character where, within a few weeks, some eighteen new-born infants developed hemorrhages at various sites — the umbilical cord, mouth, nose, skin, etc. These cases must also be considered bacterial in nature. Finally, we wish to suggest that many of the reported instances of scurvy in breast fed babies are to be regarded as cases of sepsis grafted on general malnutrition due to syphilis, tuberculosis and undernourishment, rather than as true scurvy.

CONCLUSIONS

One of the several factors in the pathogenesis of infantile scurvy is faulty diet. Pasteurized milk was found to be a contributing cause if it was not fresh — if given twenty-four to forty-eight hours after pasteurization. From this point of view milk pasteurized in the city is preferable to milk pasteurized at the creamery, which reaches the consumer much longer after the heating process. Aging seemed to

play a greater role in the production of scurvy than heating, whether the milk was pasteurized or raised to the boiling point. It was found that even raw milk on aging loses its antiscorbutic properties.

Infantile scurvy is not, however, a simple dietary disease. The diet is at fault in allowing the intestinal bacteria to elaborate toxins. It is doubtful whether the toxin is always the same, and therefore whether, from a strictly etiologic standpoint, this disorder should be regarded as an entity. Infantile scurvy is an intestinal intoxication or an autointoxication due to the overgrowth of harmful bacteria in the intestine. It is the product of an unbalanced flora which is no longer controlled by a proper dietary.

Oliguria is a common symptom of scurvy. The mild therapeutic effect of citric acid may be ascribed partly to its diuretic properties. Orange juice also was found to bring about marked diuresis.

One of the striking and important symptoms of scurvy is a susceptibility to infection (furunculosis, nasal diphtheria, "grippe," etc.). Some hemorrhages are due to this secondary infection, and are to be regarded not as scorbutic, but rather as focal complications. Other hemorrhages are truly scorbutic. Scurvy, however, is essentially a disorder characterized by malnutrition and not by hemorrhage, taking months to develop, and, from a clinical point of view, frequently latent or subacute.

Infantile scurvy occurring in epidemic form is described. This results when latent scurvy exists among a number of infants and an infectious disease (such as "grippe") is superadded.

16 West Eighty-Sixth Street.

Hess 1917

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