

## PRINCIPLES OF TREATMENT

The treatment of these cases is the hot cautery. In extensive areas such as in case 3, where the infection was progressing rapidly and was overwhelming, and where it is inadvisable to attempt to excise all the tissue, the lesion can be exposed with the endotherm knife and the tissue then dissected out or thoroughly cauterized with the hot cautery. In no instance should the scalpel be used. The use of the cautery in cases in which there is much pain is followed by marked relief of pain, which is striking.

The therapeutic action of the hot cautery is probably due not solely to the excision of the affected tissue, because if such an excision were done as for malignant tumors it would be necessary to remove at least a good portion of the aponeurosis of the abdominal wall and probably some of the muscle; for it has been shown that the streptococcus, which is the dominant element in this bacterial symbiotic relationship, penetrates beyond the apparently affected tissue.

The case of Probst and Seelig is interesting in this connection. A typical gangrenous ulcer followed an operation on the mammary gland and resisted treatment for several months while numerous therapeutic remedies, both local and general, were unavailing. Finally the disease was checked after transfusions from donors who had been vaccinated with attenuated bacteria taken from the ulcerative lesion.

In these cases in which the cautery is used it seems not only that the lymphatics and smaller blood vessels are closed by the cautery and these avenues of extension eliminated but also that a definite autogenous vaccine is formed. After a thorough application of the hot cautery there may be considered to be, roughly, three zones of tissue: one in immediate contact with the cautery in which all cells and bacteria are destroyed and disintegrated; a second zone, blending with this, in which the bacteria and tissue cells are probably killed but not disintegrated; and a third zone, external to the second, in which the bacteria are largely attenuated and possibly a few killed. This makes an ideal condition for an autogenous vaccine, and the prompt recovery and checking of the disease after a thorough application of the cautery could be attributed to this action. The treatment, then, that is strongly indicated for this symbiotic infection is the hot cautery, with the endotherm knife as an adjuvant, if necessary. In addition, continuous intravenous injection of dextrose in Ringer's solution is most helpful, and in the overwhelming fulminant type with shock, such as case 3, it is essential. In the other cases, of a milder type, it is also indicated.

Frank P. Underhill of New Haven has shown that the chief danger after burns is the loss of fluids and the electrolytes of the body. These are supplied readily without pain by the intravenous method. Dextrose solution, given in addition to the water and the electrolytes, is a decided improvement in the therapy. It has been shown by McNealy and Willems<sup>15</sup> and others that dextrose is not absorbed through the large bowel. It is difficult to utilize the stomach and small intestines for the absorption of a sufficient amount of water, and the intravenous method offers an excellent medium for furnishing nutrition, water and electrolytes at a minimum of discomfort to the patient and at as rapid a rate as the patient can stand.

617 West Grace Street.

15. McNealy, R. S.: Personal communication to the author, Feb. 8, 1930. McNealy, R. S., and Willems, J. D.: The Absorption of Glucose from the Colon, *Surg., Gynec. & Obst.* **49**: 794 (Dec.) 1929.

RECENT ADVANCES IN KNOWLEDGE  
OF SCURVY AND THE ANTI-  
SCORBUTIC VITAMIN

ALFRED F. HESS, M.D.  
NEW YORK

During the past decade the advance in our knowledge of the antiscorbatic vitamin and of experimental and clinical scurvy has not been great; it has been far less, for example, than that of vitamin D or of the vitamin B complex, which is composed of the other water soluble vitamins. In the course of this period, we have gained, however, a much clearer understanding of the antiscorbatic foods, particularly in their relation to various processes and manipulations to which they are subjected in the course of merchandising.

## PATHOLOGY OF SCURVY

In the field of pathology, great stress has been laid on the changes in the teeth. As early as 1919, it was shown by Zilva and Wells<sup>1</sup> that radical alterations in tooth structure could be brought about in guinea-pigs and in monkeys by a deficiency of the antiscorbatic vitamin. The lesions were in the nature of a fibrosis or a fibroid degeneration of the pulp. These early observations have been extended and have been made the basis of broad clinical deductions in regard to the etiology and incidence of caries. In 1924, Hoejer<sup>2</sup> of Stockholm published a report from Jundell's clinic which showed the possibility of making an early diagnosis of scurvy in guinea-pigs from the histologic examination of the teeth. He demonstrated, by means of convincing illustrations, that definite lesions of the teeth developed as early as the second week after the animals had been placed on a ration highly deficient in vitamin C. The characteristic and primary change he believed to be a development of active osteoblasts from normal active odontoblasts, with the consequent formation of bone in place of dentin. Early involvement of the teeth has also been emphasized by Wolbach and Howe<sup>3</sup> and by Meyer and McCormick<sup>4</sup> in their studies on scurvy, and their stand has likewise been supported by convincing illustrations. The dental lesions in scurvy will be referred to again in connection with a consideration of the newer symptomatology of this disorder.

One aspect of the pathology of scurvy to which particular attention has been devoted during the past few years is the changes in the vessels. In 1921, it was suggested that a "failure of the integrity of the epithelium of the blood vessels" occurred and that "this was due to a lesion of the endothelial cells or their cement substance."<sup>5</sup> A few years later, Wolbach and Howe<sup>3</sup> showed that the defect in the capillaries results from a failure of the endothelial cells to form cement substance and they concluded that the essential pathologic alteration in scurvy is "an inability of the supporting tissue to produce and maintain intercellular substances." They further maintained that this nutritional defect held true not only for the blood vessels but also for the connective tissue of various organs of the body, including the teeth. In the latter

1. Zilva, S. S., and Wells, F. M.: Changes in the Teeth of the Guinea-Pig Produced by a Scorbatic Diet, *Proc. Roy. Soc.*, series B **90**: 505, 1919.  
2. Hoejer, Axel: Studies in Scurvy, *Acta paediat. (supp.)* **3**: 8, 1924.  
3. Wolbach, S. B., and Howe, P. R.: Intercellular Substances in Experimental Scorbatus, *Arch. Path. & Lab. Med.* **1**: 1 (Jan.) 1926.  
4. Meyer, A. W., and McCormick, L. M.: Studies on Scurvy, Stanford University, Calif., Stanford University Press, 1928.  
5. Hess, A. F.: Newer Aspects of Some Nutritional Disorders, *J. A. M. A.* **76**: 693 (March 12) 1921.

they noted, on the addition of an antiscorbutic to the dietary, a change in intercellular substance from a liquid to a solid or a jell state.

Meyer and McCormick included an examination of the nervous system in their studies and found degenerative changes in the peripheral nerves and degenerative changes in the large motor cells of the anterior horn. This is the only study that has included the nervous system in its scope and is therefore of particular interest. The only report of pathologic changes of the nervous system in human scurvy is one that I<sup>6</sup> published in 1918, on focal degeneration of the lumbar cord in a case of infantile scurvy. It is highly desirable, from a pathogenic point of view, that further investigation be made regarding involvement of the nervous system, both in experimental and in human scurvy.

#### SYMPTOMATOLOGY

In regard to symptomatology it was hardly to be expected that much new data would be forthcoming, but it was to be anticipated that endeavors would be directed toward a recognition of the earliest symptoms of the disorder, of the condition designated as "latent scurvy."<sup>7</sup> This clinical condition has also been termed "praeskorbut," a designation which is not pertinent as it conveys the impression that the nutritional disturbance is of a nature different from scurvy. In connection with latent scurvy the greatest importance must be attached to the assertion that dental caries is the outstanding sign of this type of the disorder. As is well known, Hanke<sup>8</sup> and others believe that the distinctive sign of a deficiency of the antiscorbutic vitamin is caries of the teeth; in fact, that this widespread dental disorder is due mainly to a lack of vitamin C in the dietary. Accordingly, they advise that the daily dietary should include a pint of orange juice and the juice of one lemon, as well as lettuce and cabbage. In my opinion, these deductions are far too sweeping and are not supported by the geographic distribution of dental caries or by a study of individual cases, which all indicate some other dominant etiologic factor.<sup>9</sup>

#### ASSOCIATION OF SCURVY WITH INFECTIONS

Another point that has been brought into prominence in connection with adult as well as infantile scurvy is its intimate association with the infectious process. In 1917 I<sup>10</sup> stated that "one of the striking and important symptoms of scurvy is a susceptibility to infection (furunculosis, nasal diphtheria, grippe, etc.)." In this connection it may be mentioned that nasal diphtheria was noted among a group of scorbutic infants in spite of the fact that many of them gave a negative Schick reaction. Findlay,<sup>11</sup> attacking the problem from an experimental standpoint, showed that guinea-pigs which suffered from chronic scurvy and showed but few clinical symptoms manifested a decreased resistance to bacterial infection; this he attributed to degenerative changes in the bone marrow. About this time Cramer and Kingsbury<sup>12</sup> emphasized the impor-

tance of vitamin A in warding off infections, associating this susceptibility with a decrease in the number of platelets of the blood. Abels,<sup>13</sup> in a monograph on scurvy, stressed this relationship of the scorbutic state to infection, giving the name "dysergie" to the nutritional disturbance which occasions the heightened susceptibility. Recently, Minot and his colleagues<sup>14</sup> came to the conclusion that adult scurvy can be precipitated by infectious processes; in other words, that latent scurvy can by this means be changed to manifest scurvy. In general, therefore, investigations in the laboratory as well as clinical observations are in agreement in stressing the interrelationship of scurvy and bacterial infection.

#### THE CAPILLARY RESISTANCE TEST

The involvement of the blood vessels in scurvy has been stressed in connection with the newer pathology of this disorder. A clinical application of this pathologic condition is the "capillary resistance test" introduced by Hess and Fish<sup>15</sup> in 1914. This is a test of the ability of the small blood vessels to withstand increased intravascular pressure, which is brought about by means of a tourniquet applied to the arm. Clinical studies of this aspect were published by Meyer<sup>16</sup> in 1923, by Öhnell<sup>17</sup> in 1928 and by Goethlin<sup>18</sup> in 1931. The title of the latter paper, "A Method of Establishing the Vitamin C Standard and Requirements of Physically Healthy Individuals by Testing the Strength of their Cutaneous Capillaries," indicates the author's extreme point of view. He found that in Sweden, during April and May, the school children in some country districts gave a positive "capillary resistance test" in 18 per cent of the cases. In my experience there are decided individual variations in regard to the reaction to this test, so that although it is true that petechial spots are far more numerous in individuals suffering from latent or active scurvy, the reaction cannot be used as evidence of a deficiency in vitamin C intake. Occasionally edema rather than hemorrhage has been found in the scurvy of adults and of infants. The cause of these extravasations, which have been noted most often at the ankles, is not known. It would seem most likely that it is associated with a retention of sodium chloride.

#### INVOLVEMENT OF THE NERVOUS SYSTEM

In infantile scurvy there are definite clinical evidences of an involvement of the nervous system, more particularly of the vagus, as manifested by excessive rapidity of the pulse and of the respirations, symptoms that yield promptly on the addition of antiscorbutic food to the dietary. In 1925, Stewart<sup>19</sup> reported the neurologic symptoms of 150 cases of scurvy which he had observed during the World War. He recorded various indications of sensory disturbances—paresthesia of several forms, pain, hyperalgesia, patchy anesthesia on one or both legs which were symmetrical in a few cases, knee jerks which were

6. Hess, A. F.: Focal Degeneration of the Lumbar Cord in a Case of Infantile Scurvy, *J. Infect. Dis.* **23**: 438 (Nov.) 1918.

7. Hess, A. F.: Subacute and Latent Scurvy: The Cardiorespiratory Syndrome (A New Sign), *J. A. M. A.* **68**: 235 (Jan. 27) 1917.

8. Hanke, M. T.: Relation of Diet to General Health and Particularly to Inflammation of the Oral Tissues and Dental Caries, *J. Am. Dent. A.* **17**: 957 (June 17) 1930.

9. Hess, A. F., and Abramson, H.: The Etiology of Dental Caries, *Dental Cosmos* **73**: 849 (Sept.) 1931.

10. Hess, A. F.: Infantile Scurvy: V. A Study of Its Pathogenesis, *Am. J. Dis. Child.* **14**: 337 (Nov.) 1917.

11. Findlay, G. M.: The Relation of Vitamin C to Bacterial Infection, *J. Path. & Bact.* **26**: 1 (Jan.) 1923.

12. Cramer, W., and Kingsbury, A. N.: Local and General Defenses Against Infections and the Effect on Them of Vitamin Deficiency, *Brit. J. Exper. Path.* **5**: 300 (Oct.) 1924.

13. Abels, H.: Die Dysergie als pathogenetischer Faktor beim Skorbut, *Ergebn. d. inn. Med. u. Kinderh.* **26**: 733, 1924.

14. Mettler, S. R.; Minot, G. R., and Townsend, W. C.: Scurvy in Adults, *J. A. M. A.* **95**: 1089 (Oct. 11) 1930.

15. Hess, A. F., and Fish, Mildred: Infantile Scurvy: The Blood, the Blood Vessels and the Diet, *Am. J. Dis. Child.* **8**: 386 (Dec.) 1914.

16. Meyer, L. F.: Die skorbutische Diathese, *Monatschr. f. Kinderh.* **25**: 454 (March) 1923.

17. Öhnell, Harold: Experiences of Endemic, Manifest and Latent Scurvy in Sweden with Special Reference to New Methods of Diagnosing Latent Scurvy, *Acta med. Scandinav.* **68**: 176, 1928.

18. Goethlin, G. F.: A Method of Establishing the Vitamin C Standard and Requirements of Physically Healthy Individuals by Testing the Strength of Their Cutaneous Capillaries, *Skandinav. Arch. f. Physiol.* **61**: 225, 1931.

19. Stewart, R. M.: The Clinical Features of Scorbutic Neuritis, *J. Neurol. & Psychopath.* **6**: 191 (Nov.) 1925.

exaggerated or absent. This is the most complete clinical report of nervous involvement in scurvy.

## FOODS

Until about fifteen years ago the accepted dictum in regard to the relation of foods to scurvy was that a diet of dried or of canned foods led inevitably to the development of the disorder. This opinion, which was accepted and cited by medical authorities as well as by laymen, was based largely on the sad experiences which had been encountered with these foods in the rationing of armies and in the navy and mercantile marine. For a short time during the World War it was thought in this country that this deficiency had been overcome by means of dried vegetables, and, accordingly, drying plants were established for vegetables in various parts of the United States, more particularly in California. It was not long, however, before these establishments were discontinued, as it was shown that the dried product was highly deficient in the antiscorbic factor. The failures were due to the fact that the desiccating process was carried out too slowly and in the presence of atmospheric oxygen, rather than that the foods were exposed to a degree of temperature which was destructive. In eastern Europe dry leguminous pulses, more particularly peas, were steeped in water and allowed to sprout, and the sprouts were used successfully as an antiscorbic food for troops. It is of interest that Harden and Zilva<sup>20</sup> showed that the antiscorbic activity is acquired after the steeping process and before germination comes about.

Great progress has been made in regard to preserving the vitamin potency of canned foods. In 1918 it was shown that canned tomatoes retain by far the major part of their antiscorbic vitamin<sup>21</sup> and, a few years later, that dry milk, milk that had been quickly dried by the roller process, had lost but little of its scurvy protective quality. These results were surprising, especially in respect to dry milk, a product which had been subjected not only to drying but to canning and also to aging. Soon thereafter, I<sup>22</sup> demonstrated that the factor which was destructive to the antiscorbic vitamin was oxidation rather than heat and that what had been commonly regarded as the damaging effect of high temperature was largely the effect of oxidation. In the application of this principle to commercial canning the careful and consecutive studies of Kohman and Eddy and their collaborators<sup>23</sup> have been most illuminating. Biologic assays of canned foods have been carried out on the guinea-pig, making use of the basal ration which was developed and recommended in 1922 by Sherman, La Mer and Campbell<sup>24</sup> and which has the advantage of being adequate in all nutritional factors with the exception of vitamin C. Without going into detail in regard to the effect of canning on the various vegetables and fruits, each one of which manifests a certain individuality, it may be stated that it is now possible to can these foods with very slight loss of the antiscorbic factor, provided the process is carried out without subjecting the food to the deleterious effect of oxygen. The technic has even been

developed to such an extent that the so-called respiratory oxygen, in other words, the oxygen which is bound within the tissue of the vegetable or fruit, is removed or rendered inert. For example, apples are allowed to stand in salt solution before being processed in order to exhaust their "respiratory oxygen."<sup>25</sup> The high antiscorbic value of canned tomato juice compared to cabbage juice has been found by Kenny<sup>25</sup> to be due not only to its high acidity but also to its low oxidation potential. Zilva<sup>26</sup> also showed that the citrus fruits can be subjected to astonishingly long periods of heating, provided anaerobic conditions are maintained. For example, little loss of potency came about in decitrated lemon juice after autoclaving at 40 pounds pressure (143 C.) for one hour, and orange juice could be subjected for four hours under high vacuum to a temperature of from 40 to 45 C. (104-113 F.). Dried orange juice also retained almost all its antiscorbic value. The vitamin C content of the citrus fruits does not vary in potency according to acidity.<sup>27</sup>

There are a few isolated observations made in the course of the many studies of fruits and vegetables which should not be passed by without mention. A recent observation by Zilva<sup>28</sup> shows how variable is the vitamin content of foods and how necessary it is to test not only each food but each variety. For example, quantitative tests showed a remarkable difference between different varieties of apples, one variety assaying at an exceptionally high level. Again, it was demonstrated that green tomatoes ripened by ethylene, a gas which is used considerably for this purpose in commerce, did not lose their antiscorbic vitamin.<sup>29</sup> In view of the fact that canned pineapple is being used to an increasing extent, it is worth noting that Miller<sup>30</sup> found that the antiscorbic value of this food is only slightly less than that of the fresh fruit.

There is little to be added in regard to our knowledge of the antiscorbic potency of milk. As is well known, its potency is dependent entirely on the vitamin content of the food or fodder of the animal. It was therefore of interest and of practical importance from a dairy standpoint to learn from MacLeod<sup>31</sup> that "by including an ensilage of good quality in the ration, the antiscorbic potency of the milk may be maintained at a high level." Investigations preceding the era which is being considered demonstrated that raw milk contains a moderate quantity of vitamin C and that it loses from one fourth to one third of this factor in the course of ordinary pasteurization. It was also shown that traces of copper bring about rapid destruction of the antiscorbic vitamin in the course of the heating or pasteurizing process,<sup>32</sup> a result which is due to its

25. Kenny, C. L.: A Study of Thermostability of Vitamin C, Dissertation, Columbia University, New York, 1926.

26. Bracewell, Mary F., and Zilva, S. S.: Vitamin C in the Orange and the Grapefruit, *Biochem. J.* **25**:1081, 1931.

27. Zilva, S. S.: The Antiscorbic Fraction of Lemon Juice: VII, *Biochem. J.* **22**:779, 1928.

28. Bracewell, Mary F.; Kidd, Franklin; West, Cyril; and Zilva, S. S.: The Antiscorbic Potency of Apples: II, *Biochem. J.* **25**:138, 1931.

29. Clow, B., and Marlatt, A. L.: Studies of Vitamin C in Fresh and Canned Tomatoes, *J. Agric. Research.* **40**:767, 1930.

30. Miller, C. D.: Vitamin C in Fresh and Canned Pineapple, *J. Home Econ.* **17**:377, 1925.

31. MacLeod, Florence L.: Antiscorbic Vitamin Content of Milk of Stall-Fed Cows Throughout a Year, *J. A. M. A.* **88**:1947 (July 18) 1927.

32. Hess, A. F.: The Destruction of the Antiscorbic Vitamin in Milk by the Catalytic Action of Minute Amounts of Copper, *Proc. Soc. Exper. Biol. & Med.* **19**:119, 1921. In a paper published in 1762, entitled "That the Use of Copper Vessels in the Navy is One Principal Cause of the Sea Scurvy," Travis (London Medical Observations and Inquiries **2**:1, 1762) stated: "The number of ships sent to sea from this place is about 200 sail and we employ about 3,000 seamen and boys. On board of these, iron pots are in general use, and we have no instance of any one having the symptoms called highly scorbutic, except on some few of the larger ships on which coppers are used."

20. Harden, A., and Zilva, S. S.: Investigations of Barley, Malt and Beer for Vitamins B and C, *Biochem. J.* **16**:1129, 1924.

21. Hess, A. F.: Canned Tomatoes as an Antiscorbic, *Proc. Soc. Exper. Biol. & Med.* **15**:96, 1918.

22. Hess, A. F.: The Destructive Effect of Oxidation on Antiscorbic Vitamin, *Proc. Soc. Exper. Biol. & Med.* **18**:143, 1921.

23. Kohman, E. F.; Eddy, W. H., and Carlsson, V.: Vitamins in Canned Foods: II. The Vitamin C Destructive Factor in Apples, *J. Indust. & Engin. Chem.* **16**:1261, 1924. (Many other papers in this journal.)

24. Sherman, H. C.; La Mer, V. K., and Campbell, H. L.: The Quantitative Determination of the Antiscorbic Vitamin (Vitamin C), *J. Am. Chem. Soc.* **44**:165, 1922.

catalytic action. Recently, a careful study by Schwartz and his co-workers<sup>33</sup> on the effect of vitamin C content of milk in the presence of certain metals showed that copper and tinned copper were not suitable metals for pasteurizing equipment, whereas aluminum and glass are innocuous. The interesting suggestion was made that anaerobic pasteurization might be of practical value on account of the protective environment which it affords.

#### THE ANTISCORBUTIC VITAMIN

As stated, the advance in knowledge of the antiscorbatic vitamin has been very slight, especially as compared to the rapid strides that have been made during the past five years in the chemistry of the antirachitic vitamin. In 1921, Bezssonoff<sup>34</sup> carried out a series of experiments with cabbage juice in which he was able to remove some of the active material by means of neutral lead acetate. The main result of his experiments was the development of a specific color test for vitamin C and its recommendation as a substitute for the biologic assay on the guinea-pig. The test substance is essentially the Folin-Denis phenol reagent, but subsequent experience with this reagent has proved it to be unreliable. Some of the most interesting studies in this field have been reported by Zilva and his colleagues<sup>35</sup> at the Lister Institute. They removed the sugar from orange juice by means of fermentation with yeast and then precipitated the vitamin with basic lead acetate. With this concentrate they carried out various physicochemical experiments by means of adsorption and diffusion through collodion membranes of varying permeabilities and were able still further to concentrate the antiscorbatic principle. One of the main results of their work was the demonstration of "a reducing principle" of importance in connection with the activity or inactivity of the antiscorbatic vitamin. They found that this reducing substance exerts a protective action on the vitamin and that when it is removed in the course of chemical fractionation of vitamin C there is a consequent loss of the vitamin; in other words, that this substance protects the vitamin in its natural medium. In another interesting experiment they showed that the addition of autoclaved juice to unheated lemon juice, which had been decitrated by means of calcium carbonate, accelerated the loss of "the reducing principle" and of antiscorbatic activity when the juice was stored at  $p_H$  7. Smith and King<sup>36</sup> have just reported that they prepared an active fraction of lemon juice in which the amount of total solids was 0.09 mg. per cubic centimeter of equivalent of the original juice; in other words, they were able to concentrate the material more than 10,000 times. It is of interest that this fraction showed a reducing value equivalent to that of dextrose.

Nothing could illustrate the sudden and rapid advances which are occurring in the field of vitamin investigations better than the fact that within the past month, in other words, within the period when the foregoing lines were written, a greater advance in our knowledge of the antiscorbatic factor has been reported than throughout the entire preceding decennium. Rygh

33. Schwartz, E. W.; Murphy, F. J., and Cox, G. J.: Effect of Pasteurization on the Vitamin C Content of Milk in the Presence of Certain Metals, *J. Nutrition* 4: 211 (July) 1931.

34. Bezssonoff, N.: Sur une réaction colorée commune aux extraits antiscorbaticque et à l'hydroquinone, *Compt. rendu Acad. d. sc.* 173: 466, 1921.

35. Zilva, S. S.: The Antiscorbatic Fraction of Lemon Juice, *Biochem. J.* 21: 689; Hoyle, Edward; and Zilva, S. S.: *Ibid.* 21: 1121, 1927. Zilva, S. S.: *Ibid.* 23: 1199, 1929.

36. Smith, F. L., and King, C. G.: The Preparation and Storage of Vitamin C Concentrates from Lemon Juice, *J. Biochem.* 94: 491 (Dec.) 1931.

of Uppsala, and his colleagues,<sup>37</sup> have stated not only that they have isolated vitamin C but that they have been able to synthesize it. Their research started with the conception that, if orange juice was carefully neutralized, it might be possible to extract the active principle from it by means of ether. By this procedure they obtained a considerable amount of crystalline substance which, on further investigation, proved to be the well known mildly toxic alkaloid of opium, narcotine ( $C_{22}H_{23}NO_7$ ). This substance, however, was found to be devoid of antiscorbatic potency. On extracting the juice from unripe oranges they obtained a far greater quantity of narcotine, as much as 600 mg. from 10 liters of juice; as the fruit ripens, the narcotine disappeared. The alkaloid was obtained likewise in large amounts from tomatoes, potatoes and white cabbage but only in small quantity from milk. On irradiating narcotine with the rays from a mercury vapor lamp they developed an active antiscorbatic preparation, which prevented scurvy in guinea-pigs in a daily dosage of about 1 mg., although it failed to prolong life to a marked degree. Furthermore, on making various synthetic products of narcotine they found that several could be elaborated which were antiscorbatic, the most potent being methylnarcotine, which afforded protection when as little as 0.02 mg. was added to the basal ration. This experimental work has not been substantiated, but it is clear that we are on the threshold of a new era in the realm of experimental scurvy, one which will lead probably to the elucidation of many aspects which have been unsatisfactory and contradictory in the etiology, symptomatology and therapy of this disorder as it is manifested in the experimental animal and in man.

King and Waugh<sup>38</sup> have just reported that, on continuing their experiments with the concentration of vitamin C from lemon juice, they have obtained a substance that is identical with hexuronic acid, which has been found in the suprarenal cortex, cabbage and other sources. Feeding approximately 0.5 mg. daily protected guinea-pigs receiving a diet free from vitamin C. Although this work is too new to have been substantiated, it seems most promising. It is clear that this vitamin is about to be reinvestigated from a biologic and a chemical point of view.

Recently an international conference was held in London to establish uniform standards for the various vitamins. The unit for the antiscorbatic vitamin was laid down as the vitamin C activity of 0.1 cc. of fresh lemon juice of the lemon *Citrus limonum*. This standardization makes it possible in future to compare investigations and assays in this field which are carried out in laboratories in different parts of the world.

#### PATHOGENESIS

As usual, pathogenesis presents the greatest difficulty. In this respect the problem is no different for vitamin C than in relation to any other of the vitamins. Although from time to time doubt has been cast on the simple and unalloyed nature of scurvy and of vitamin deficiencies as the underlying cause of the various avitaminoses, little attention has been paid to these doubts and misgivings. In 1917, in a study on the

37. Rygh, Ottar; Rygh, Aagot; and Laland, Per: Chemische Untersuchungen über das antiscorbaticque Vitamin: I. Laland, Per: Versuche zur Isolierung des Narkotins aus verschiedenen Vegetabilien. Rygh, Ottar; and Rygh, Aagot: Chemische Untersuchungen über das antiscorbaticque Vitamin: II. Ueber Narkotin und dessen Abkömmlinge als Antiscorbaticque, *Ztschr. f. physiol. Chem. (Hoppe-Seyler's)* 204: 105, 112, 114, 1932.

38. King, C. G., and Waugh, W. A.: The Chemical Nature of Vitamin C, *Science* 75: 357, 1932.

pathogenesis of scurvy, I<sup>10</sup> made the following statement: "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 strictly, from an etiologic standpoint, this disorder should be regarded as an entity." Whether this point of view requires modification will depend on subsequent investigations, but in the main it would seem to accord with clinical and experimental observations. Some recent work by Kollath and his colleagues<sup>39</sup> is of interest in this connection. In the first place, they corroborated McCollum's observation that, although polyneuritis is induced in rats as the result of a scorbutic diet, the pathologic lesions of the bones are those of scurvy. They showed, furthermore, that without any basic change in the dietary they could induce scurvy or beriberi at will. By incorporating peanut oil instead of cottonseed oil in the ration they were able, for the first time, to bring about, in rats, clinical scurvy associated with multiple hemorrhages, and were able to change this result and induce beriberi in the majority of the animals merely by adding alkaline hematin to the dietary. This change they attribute to an oxidation within the intestine of the unsaturated fatty acids of the peanut oil, brought about by the catalyzing action of the hematin. They believe that beriberi and scurvy have a common metabolic cause and that the vitamins are merely of relative importance—whether the one or the other disorder develops, depending on minor deficiencies in the dietary or on harmful additions. These results in animals recall a clinical observation made several years ago by Darling<sup>40</sup> that among some African Negroes a diet that caused scurvy in one set of men caused neuritis in others. They accord also with clinical experience in regard to the unaccountable irregularities in the course of scurvy. Scurvy may fail to recur although the diet is the same as that which led originally to the disorder.

In connection with these considerations it is probably not without significance that a diet which causes scurvy in the guinea-pig leads to polyneuritis in the fowl, and that of two herbivora as closely related as the guinea-pig and the rabbit, the former is extremely sensitive to scurvy whereas the disorder can be induced in the latter only with the greatest difficulty. It may be added that Hauge and Carrick<sup>41</sup> have noted that, although the egg of the hen does not contain vitamin C, chicks develop normally without the addition of this vitamin to their ration. They attribute this to a synthesis of the nutritional factor.

#### INCIDENCE OF SCURVY

During the War, scurvy increased in infants and adults among both the military and the civilian population, but during the past decade it has been no more frequent than in prewar times. In Leningrad, however, in a three year period ending in 1924, 186 cases of scurvy were observed in the children's clinic, and the mortality was 16 per cent.<sup>42</sup> In New York City cases are exceptional, for it has become almost routine to include orange juice or tomato juice in the dietary of the infant, and adults partake of potatoes, fruit or vegetables throughout the year. Economic conditions

have, however, always had an effect on the incidence of scurvy, and it is quite possible, if not probable, that the economic depression in this country and abroad may entail an increase in latent and manifest scurvy in adults as well as in infants.

16 West Eighty-Sixth Street.

## PAINLESS JAUNDICE

ITS DIFFERENTIAL DIAGNOSIS BY THE GALACTOSE  
TOLERANCE TEST

HARRY SHAY, M.D.

AND

EUGENE SCHLOSS, M.D.

PHILADELPHIA

The difficulties encountered in any functional test studies are particularly accentuated in those concerned with the liver. This is largely due to the fact that nature has entrusted to the liver a multiplicity of functions not equaled by any single organ. These numerous activities, widely dissociated in character, give rise to the necessity for the many liver tests that have been devised. The application of these tests is beset with further difficulties dependent on the peculiar physiologic activity of the liver. The continued functioning of this organ being vitally necessary,<sup>1</sup> it has been endowed with an adequate reserve<sup>2</sup> and a markedly high regenerative capacity. Some idea of the regenerative ability of the liver cells may be obtained from the experiments of Mann and Bollman,<sup>3</sup> who found that the removal of 70 per cent of the liver of the normal dog was followed in a few weeks by regeneration of the remaining 30 per cent to approximately the preoperative level. It is these factors which offer the greatest difficulty both in the experimental production of chronic hepatic insufficiency and in the evaluation of function tests in clinical chronic hepatic damage. If one adds to the aforementioned difficulties the problems of the utilization of sugars by the tissues, the rôle of the endocrines in sugar metabolism, the inaccuracy of chemical methods for the determination of various sugars in the blood, and the relation of the kidney threshold to sugar excretion, one can appreciate a few of the pitfalls that have hindered attempts to study the carbohydrate function of the liver as a measure of that organ's activity.

The discovery of the carbohydrate function of the liver by Claude Bernard stimulated many attempts to utilize that function as a measure of the liver's working capacity. The resulting controversy between the German and the French schools during the latter part of the last century left this problem in a very doubtful state of utility. Interest was reawakened, however, by the work of Strauss<sup>4</sup> in 1901, in which levulose was introduced as an hepatic test substance; the conflicting opinions of other observers were reconciled on the basis of the variations in types and amounts of the test sugars previously used, and the levulose tolerance test has undoubtedly remained the favorite among the carbohydrate function tests of the liver.

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