

STUDIES RELATING VITAMIN C DEFICIENCY TO RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS; EXPERIMENTAL, CLINICAL AND GENERAL CONSIDERATIONS *

II. RHEUMATOID (ATROPHIC) ARTHRITIS

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A border-land between rheumatic fever and rheumatoid arthritis has long been recognized. Particularly in young adults clinical distinction may prove difficult or one may find an apparently typical rheumatic fever with carditis progress into a characteristic rheumatoid arthritis. Klinge and Grzimek¹ find that although acute and subacute rheumatic fever and chronic polyarthritis are usually easily differentiated, both disease pictures are so closely bound together in the arthritic and general pathology that a "rheumatic" basis may be assigned to both. Dawson² has lent further support to the concept of a relationship of the two diseases in showing that the early pathological change found in the subcutaneous nodules of rheumatic fever and rheumatoid arthritis, are essentially identical. This evidence, together with encouraging early observations made on the joints in scurvy^{3,4} led to a rather extensive study of the scorbutic arthropathy. It is the purpose of this paper to report the findings of this study and to draw attention to a rather convincing amount of data suggesting that vitamin C under-nutrition may be an etiological factor in at least some of the cases classified as rheumatoid arthritis.

EXPERIMENTAL METHODS

The methods employed consisted briefly in maintaining guinea pigs for rather prolonged periods of time on a basic vitamin C free diet,† supplemented with inadequate amounts of vitamin C. To study the influence of infection, parts of each experimental series were infected. Control groups

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† The basic diet used is as follows:

	Per cent
Ground rolled oats and bran—equal parts by volume	56
Powdered skimmed milk (baked at 110° for 2 hours)	30
Butter fat	10
Sodium chloride	0.5
Osborne-Mendel salt mixture	1.0
Dried yeast	1.5
Cod-liver oil (standardized)	1.0

Care is used in securing a thorough mixture of the above ingredients. Guinea pigs eat this diet well and, with adequate vitamin C supplement, grow and thrive.

of course, were maintained on the basic diet adequately supplemented with vitamin C and subjected to the same infection. The material of this study comprises 12 series of experiments. Inasmuch as pathological observations are in essential agreement in the various experiments, no attempt will be made to report individual experiments. Sufficient detail will be found in the appended protocols, to guide anyone interested in repeating the experimental work. No sharp line can be drawn between the experiments pertaining to rheumatic fever and to the chronic arthritis. An over-lapping occurs here as is observed clinically.

THE ARTHRITIS OF SUBACUTE OR CHRONIC SCURVY

One of the first objective manifestations of vitamin C deficiency in the guinea pig is an arthropathy which is characterized by pain, swelling and limitation of movement in multiple joints. The joints exhibiting the most obvious involvement, and the usual, though not invariable sequence, are



FIG. 1. Diffuse fusiform swelling of the wrists, an early manifestation of vitamin C deficiency in the guinea pig.

knees, wrists, and elbows. These have been most carefully studied, but it is probable that no joints are immune. Figure 1 illustrates a characteristic appearance of an early arthritic change with a fusiform swelling about the wrists.

THE EARLY CHANGES IN SCORBUTIC ARTHROPATHY

An exhaustive study has not been made of the earliest changes in the scorbutic arthritis. However, joints of several animals have been inspected shortly after the onset of stiffness and swelling. The periarticular tissues are seen to show an edematous, hemorrhagic appearance. Microscopically, red blood cells and serum are found, spreading apart connective tissue cells, and frequently, relatively broad hyaline streaks of a peculiarly packed fibrin are seen. At this time or shortly later, the connective tissue cells begin actively to proliferate, the hemorrhagic appearance subsides and we see an imperfectly vascularized and frequently edematous granulation tissue thickening the capsule and obscuring the underlying tendons and bony prominences.

THE ARTHROPATHY OF SUBACUTE OR CHRONIC SCURVY

A much more extensive material has been studied in the later stages of the scorbutic joint disability. For convenience and clarity, it is best to consider separately the changes in the various anatomical structures forming and surrounding the joint.

Synovial Proliferation and Pannus Formation. A proliferative reaction of the synovial membrane is an almost constant finding. Usually associated with the synovial proliferation and frequently merging with the proliferating cells is a hyaline "fibrinoid" material. Figure 2 illustrates a typical reaction of this type. No sharp distinctions can be drawn between cells clearly recognizable as synovial and less differentiated connective tissue cells which, intermingled with the fibrinous material, extend from joint recesses as long tongue-like processes into the joint cavity and over the articular surfaces. Figure 3 shows the detail of such a fibrous and "fibrinoid" pannus.

Subsynovial and Peritendinous Lesions. The connective tissue beneath the synovial membrane and that about the tendons inserting around the joint present analogous changes. Here again, small extravasations of blood, streaks of fibrin and a reactive hyperplasia of connective tissue cells contribute further to the swelling deformity and limitation of movement in the joint.

Articular Cartilage. In addition to diffuse thinning, a retrogressive change, apparently a de-differentiation of areas of the articular cartilage, is not uncommonly seen. In places the surface of the articular cartilage is replaced by undifferentiated and at times vascularized connective tissue. The pannus described is, in some instances, adherent to the articular surfaces. The retrogressive change at the surface of the articular cartilage and apparent "perichondral" proliferation are shown in figure 4.

Rarefaction of Bone. Thinning of bone trabeculae is characteristic of chronic vitamin C deficiency. This rarefaction of bone involves apparently the entire skeleton but is most prominent at the bone ends. The change is

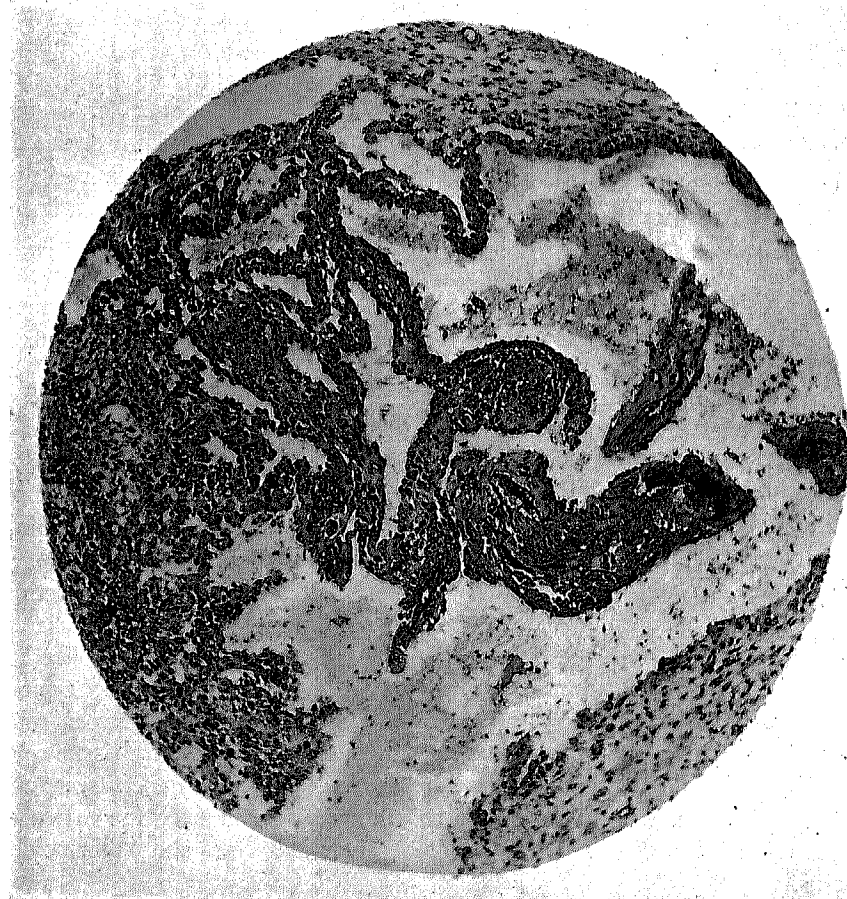


FIG. 2. A moderately intense proliferation of the synovial membrane from a recess in the knee joint of a guinea pig subjected to a subacute vitamin C deficiency and infection (beta streptococcus). $\times 200$.

clearly evident in microscopic sections (figure 5), and has been repeatedly demonstrated by roentgen-ray examination. Figure 6 illustrates this change.

Muscle. Some degree of muscle atrophy and degeneration is also a characteristic effect of prolonged vitamin C deficiency. An interstitial edema of the muscle is frequently seen to contribute to the periarticular swelling. In some of the more severe deficient states, hemorrhagic stippling of the muscle may occur. Some degree of muscle atrophy or degeneration is almost regularly found. Occasionally a widespread muscle degeneration dominates the pathologic picture. It would appear that this occasional severe myopathy is an effect of capillary hemorrhage and consequent cellular anoxemia.

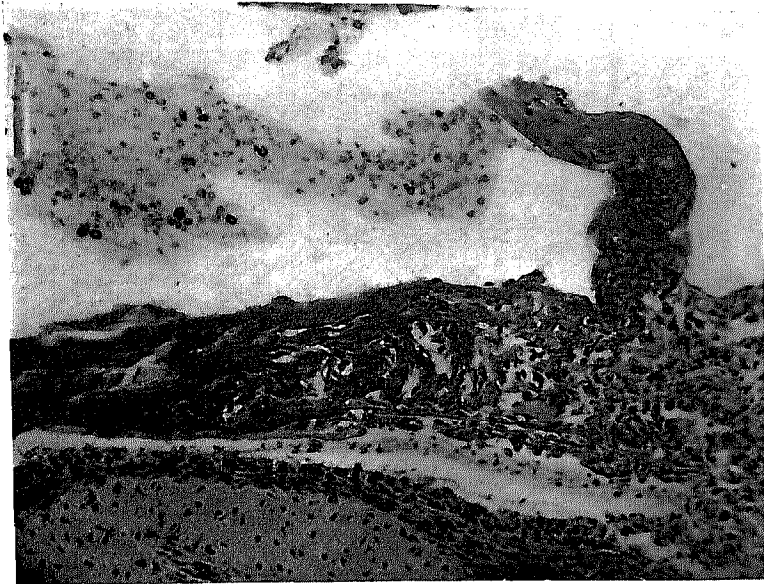


FIG. 3. Fibrous and "fibrinoid" pannus extending from a joint recess of the knee over the articular cartilage. Relatively acute scurvy and bronchopneumonia (*B. bronchisepticus*). The fibrinous material shows as grayish-black lines in microphotograph. $\times 200$.

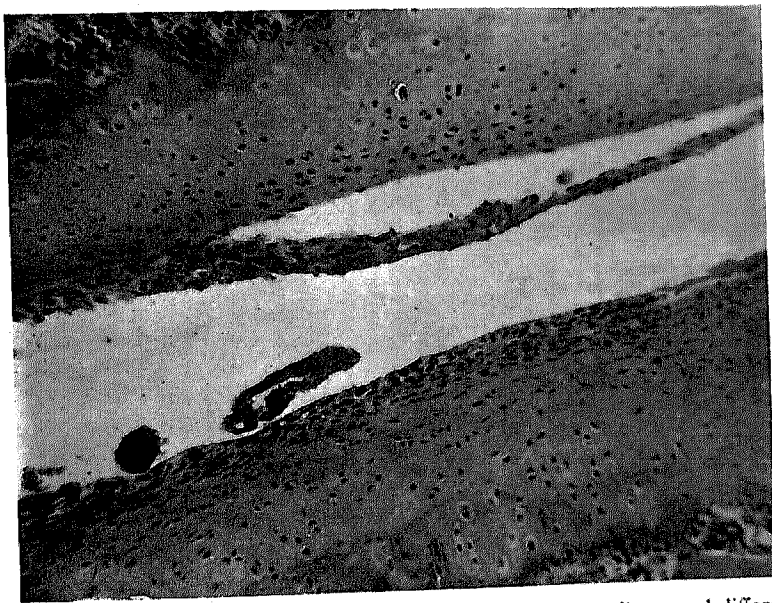


FIG. 4. Showing a retrogressive change in the articular cartilage, a dedifferentiation of the surface cells at one side and an apparent perichondrial proliferation with an associated fibrinous material at the opposite surface. Subacute scurvy and infection—duration 48 days. Developed spontaneous bronchopneumonia (*B. bronchisepticus*) on the twenty-fifth day. $\times 200$.

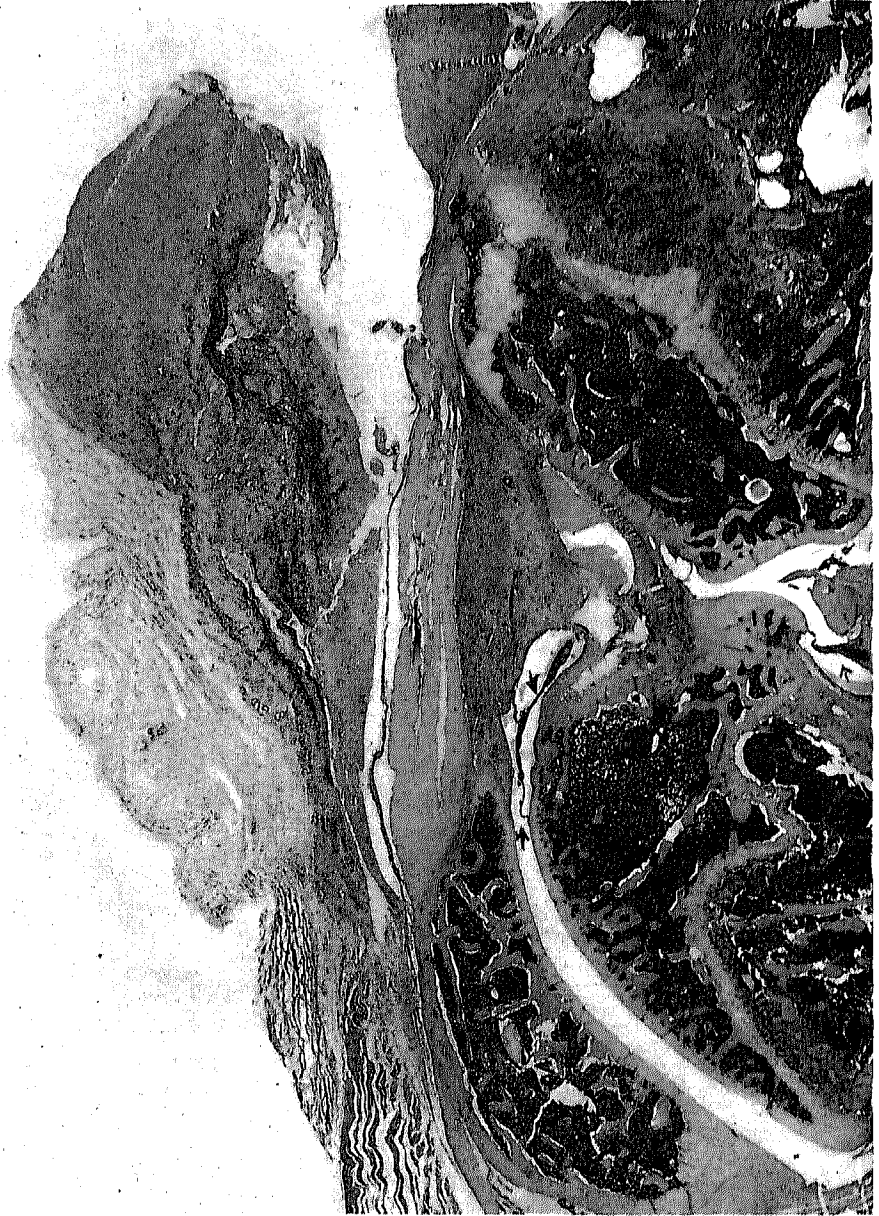


FIG. 5. Showing in low magnification the characteristic changes in the scorbutic arthropathy. The early pannus extending from joint recesses is indicated by the arrows. The thinning of the bone trabeculae may be seen, and the marked capsular thickening is evident. X 18.

Periarticular Reactions—Subcutaneous Nodules. The reactions in the capsular tissues are, perhaps, of greatest interest. The early sanguinous edema has been noted. Somewhat later, the capsular connective tissue undergoes a marked proliferative reaction. Commonly, streaks of hyalinized fibrin lie in intimate association with the reactive connective tissue. The tissue, on section, often shows a striking edema. Somewhat later, a

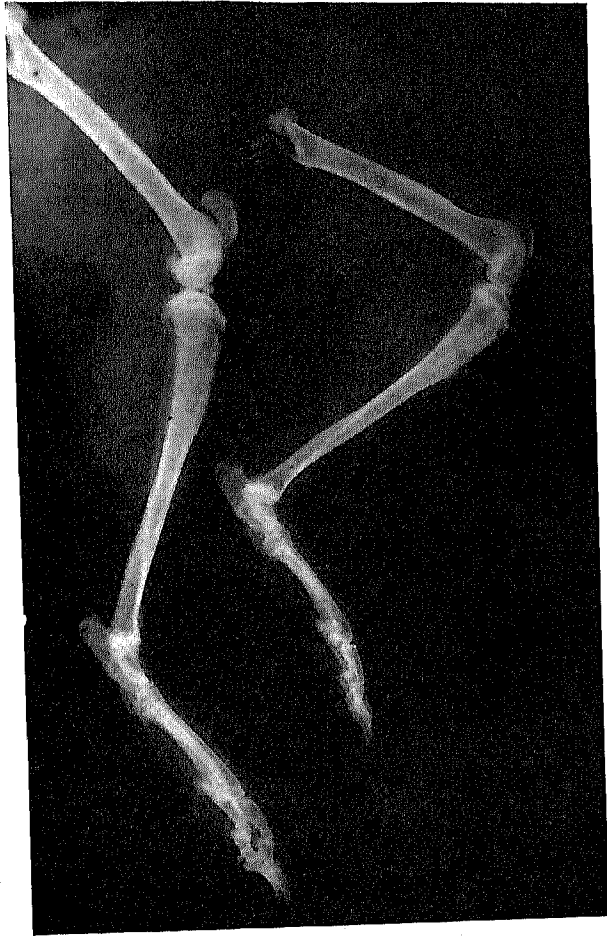


FIG. 6. This x-ray shows the hind leg of a control animal on the left, contrasted with a vitamin C deficient animal on the right. The excised limbs were exposed simultaneously; both were in an extended position. The limitation of extension is apparent in the scorbutic joint. The diminished density of the scorbutic bone, particularly at the ends about the knee joint, is clearly shown. This observation has been repeatedly verified.

gradual diminution of the periarticular thickening may occur, coincident with the shrinkage of the connective tissue. Figure 5 illustrates the topography of the intra- and periarticular lesions. A most interesting observation is the not infrequent development of discrete circumscribed fibrous

tissue nodules beneath the skin about the joints. Sometimes they are moveable beneath the skin and at other times are found more or less attached to an underlying bony prominence. The knee joint shown in figure 7 shows two such subcutaneous fibrous nodules as well as the thickening and deformity of the joint produced by scurvy. The position of the joint shows the limitation of extension. Microscopic sections of the subcutaneous nodules show an edematous, cellular, fibrous tissue, usually associated with



FIG. 7. A striking scorbutic arthropathy knee joint photographed in an extended position, showing limitation of extension, diffuse fibrous tissue thickening about the joint and two fibrous subcutaneous nodules. Uncomplicated vitamin C deficiency. Duration of experiment—70 days. Degree of deficiency, moderately severe.

irregular strands of brilliantly eosinophilic hyalinized fibrin (figure 8). The hyaline fibrin is in intimate association with connective tissue cells, and appears to correspond to the "fibrinoid" degeneration of Klinge.⁵ The experimentally produced subcutaneous nodules resemble most closely the pathologic picture of the subcutaneous nodules of rheumatic fever and the earlier nodules of rheumatoid arthritis, excellently described and illustrated by Dawson.²

THE EFFECT OF INFECTION SUPERIMPOSED ON THE CHRONIC SCURVY

The arthritic pathology described occurs in the absence of any introduced or demonstrable infection. Some infections, however, have been found to accentuate and accelerate the pathological process. This influence is clearly shown in the following experiment.



FIG. 8. A portion of an experimental subcutaneous nodule developed in an animal subjected to chronic vitamin C deficiency and infection. Streaks of a brilliantly eosinophilic hyalinized fibrin together with a reactive hyperplasia of imperfectly vascularized connective tissue constitutes the structure of this lesion, and corresponds closely to the rheumatic nodule. $\times 400$.

Experimental Series 14.

Nov. 1, 1934: A group of 13 animals were placed on the basic diet with an adequate daily supplement of orange juice (4 c.c.). The animals were in groups in three cages. Nov. 23, 1934: One animal in a cage of five developed a spontaneous respiratory infection, which was later determined to be due to *B. bronchisepticus*. Four days later, four other animals in the cage developed the same type of infection. Eight other animals in two other cages showed no evidence of infection. At this stage, five non-infected animals were placed in a larger cage with the four infected animals, and the group was transferred to a separate room. Of these animals, five were placed on a scorbutic régime, and four continued to receive 5 c.c. orange juice daily. Four animals were maintained unexposed to infection and subjected to the same scorbutic régime. In this instance, the scorbutic régime consisted of total deprivation of vitamin C for 18 days beginning Nov. 29, then a supplement of 1 c.c. on alternate days for 16 days, when the experiment was concluded. The five scurvy and four control animals in the infected cage all showed evidence of pulmonary infection. The scurvy animals exposed to infection all developed frank arthritic manifestations in from 10 to 15 days with an average time of onset 13 days after the deprivation of vitamin C. The non-infected scorbutic animals in this series showed

no arthritic manifestations for periods of 24 to 32 days, with an average time of onset of 31 days. Further, the arthritic manifestations in the group exposed to both scurvy and infection were clearly more severe than those subjected to scurvy alone. The animals exposed to the infection, but given an adequate orange juice supplement, although developing infection, showed no arthritic manifestations.

It would appear quite evident that the infection, in this instance, augmented the scorbutic effect in development of the arthritic lesions. Essentially similar observations have been made with other experimental infections. In other instances, however, this has not been apparent. It would seem that the type and virulence of the infection are of importance in this relationship.*

SUMMARY OF THE PATHOLOGICAL CHANGES IN THE SCORBUTIC ARTHROPATHY

The arthritis of subacute or chronic scurvy, uncomplicated or with superimposed infection, is characterized within the joint by synovial proliferation and "fibrinoid" and connective tissue pannus formation. The capsular, peritendinous and intermuscular tissues show fibrin deposition, and reactive hyperplasia of an imperfectly vascularized connective tissue. These changes contribute to pain, swelling and limitation of movement or effectual ankylosis in multiple joints. Striking lesions, frequently observed, are subcutaneous nodules histologically characterized by streaks of fibrin and reactive hyperplasia of connective tissue, and bearing a close resemblance to "rheumatic" nodules. Muscle atrophy and degeneration are regularly observed in the scorbutic arthritis. A general skeletal rarefaction develops, which is most marked at the bone ends. Certain infections accelerate and intensify the arthritic process, while others do not.

REPRESENTATIVE PROTOCOLS

Series 7. No. 189. Received basal diet plus adequate orange juice supplement for 15 days. 6/1/33 to 6/8/33, no orange juice. 6/8/33 to 6/20/33, 1 c.c. daily. 6/21/33 to 6/26/33, 0.5 c.c. daily. 6/27/33 to 7/16/33, 1 c.c. daily and 7/16/33 to 8/2/33, 0.5 c.c. daily. On 6/16/33 the animal was infected by inoculation of a broth culture of beta streptococcus (source spontaneous lymphadenitis of guinea pig). The inoculation was made into the skin of the left groin, and the animal developed a local skin infection and lymphadenitis. *Course:* 6/24/33, the left knee is stiff with limitation of extension; four days later, the right knee also stiff. 7/21/33, both knees are stiff and swollen. 7/25/33, the elbows are also swollen. 8/2/33, animal sacrificed. *Pathological notes:* General nutrition is fair. The mucous membrane of the bladder is hemorrhagic. A small abscess is present

* A few observations suggest that vitamin C deficiency may produce in the joints a locus of diminished resistance to the actual lodgement of bacteria and so predispose to the development of a truly infectious (suppurative) arthritis. This is illustrated by an observation on a guinea pig in Experimental Series Number 12. This animal was in a group subjected to chronic vitamin C deficiency, but had exhibited swelling of joints, particularly of one knee, that was much more marked than in the other members of the series. The temperature was elevated. At autopsy, an acute suppurative arthritis was evident in the most swollen knee. Cultures of the spleen and inguinal lymph node yielded a green streptococcus.

between the liver and the diaphragm. A little hemorrhage is seen over and under the right knee. This joint shows capsular thickening, synovial proliferation and early pannus formation.

Series 8. No. 201. This animal was one of a group subjected to vitamin C deficiency for a period of approximately 41 days. These animals received 1 c.c. of orange juice three times a week during the course of the experiment. Weight at onset of the experiment, 8/17/33, 374 grams. *Course:* 9/14/33, slight thickening of the tissues about the knees first noted. 9/20/33, slight stiffness and thickening of the knees, no swelling. 9/28/33, weight, 248 grams. Knees thickened and stiff. Animal sacrificed. *Pathological notes:* Moderate thickening of the capsule of the right knee. Moderate congestion and hemorrhagic stippling of the bladder mucous membrane.

Series 8. No. 210. This animal was one of a group in the same experiment subjected to the same dietary régime but also to infection with a hemolytic staphylococcus. This animal as the others of the group showed a more marked arthropathy than the animals subjected to scurvy alone, even though the local reaction at the site of infection was quite mild. *Course:* 9/14/33, knees stiff and slightly thickened. On this date the animal was infected by intracutaneous inoculation with a broth culture of hemolytic staphylococci into the skin of the neck. A mild non-suppurative cervical adenitis resulted. 9/20/33, the right knee is definitely swollen. 9/28/33, both knees thickened, stiff and swollen. Animal sacrificed. Some hemorrhage in chest wall. Right knee shows considerable capsular thickening composed of a brownish granulation tissue. There are areas of hemorrhage in this tissue. The muscle below the knee appears edematous and shows some recent hemorrhage.

Series 9. No. 247. This animal was placed on the basal diet 10/25/33. For the first 20 days a total supplement of 8 c.c. of orange juice was given. At this time, 11/15/33, the animal exhibited swelling and stiffness of both knees and tenderness of the wrists. For the next two and one-half months, the animal received alternately adequate and inadequate amounts of orange juice, the average daily intake being 1.7 c.c. Infection was introduced (beta hemolytic streptococcus) into the skin of the neck on 12/17/33. After 2/7/34, the animal received 1 c.c. of orange juice daily until death on 4/30/34, approximately six months after the onset of the experiment. *Course:* The general nutrition of the animal remained fair, and more or less arthritic disability was present in the knees, wrists and elbows throughout the experiment, with several episodes of swelling. *Pathological notes:* At autopsy, a fibrous nodule was found near the left elbow. The knee and elbow joints on section showed bone atrophy and synovial proliferation. The elbow in addition showed irregularity of the articular surface and apparent perichondrial proliferation. The subcutaneous nodule showed hyalin streaks of fibrin and reactive hyperplasia of the connective tissue.

Series 15. No. 368. Animal placed upon basal diet 11/20/34, and maintained with an adequate daily supplement of orange juice (4 c.c.) to 12/4/34, when the supplement was entirely removed for 13 days. Then animal received orange juice 1 c.c. on alternate days until 1/7/35 when sacrificed. *Course:* The temperature record indicated that the animal had developed a spontaneous infection about 12/14/34. Swelling of the knees was noted 12/15/34. On 12/24/34 the knees were swollen and tender, and the elbows were tender. *Pathological notes:* Autopsy revealed an extensive bronchopneumonia (*B. bronchisepticus*). The costochondral junctures were moderately thickened. The capsular tissues of the right knee were distinctly thickened with a brownish-red granulation tissue. There was no evidence of fresh hemorrhage. A protruding nodule of granulation tissue was found at the inner aspect of the right elbow. Sections of the knee

showed fibrous and fibrinous pannus, buckling of the cartilage and fibrous tissue thickening of the capsule. The elbow showed a broad fibrinous and fibrous tissue pannus.

Series 15. No. 376. Same series and dietary régime as 368, without however any evidence of infection. The animal survived until sacrificed on 1/31/35. *Course:* General condition and nutrition remained good. The animal first developed tenderness of knees without any swelling on 12/14/34. On 12/21/34, the knees were tender and slightly swollen, and the left wrist was swollen and tender. No elevation of temperature. On 1/31/35, the animal showed stiff, thickened and tender knees with subcutaneous nodules on both knees (see photograph in text). *Pathological notes:* The left knee showed diffuse fibrous tissue thickening of the capsule, with in addition two subcutaneous nodules. The periarticular tissues were edematous and congested. The right knee showed a similar appearance. One subcutaneous nodule was present. The capsular tissue of the right knee was 1 mm. thick. The left wrist also showed periarticular thickening.

FUNDAMENTAL SIMILARITIES OF THE EXPERIMENTAL LESIONS TO THOSE OF RHEUMATOID ARTHRITIS

One familiar with the pathology of rheumatoid arthritis will at once recognize certain basic similarities of the experimental arthritis described, to this condition. The study of Nichols and Richardson,⁹ on the pathology of chronic arthritis, remains a classic. Particularly with respect to rheumatoid arthritis, relatively little has been added to their original observations. The work of Fisher⁷ has served to confirm and in some respects extend their observations. The essential changes can be no more clearly or succinctly given than in the words of Nichols and Richardson, who in referring to proliferative arthritis (rheumatoid) say: "In this type of joint lesion the primary change occurs as a proliferation of the synovial membrane and the perichondrium of the articular cavity, combined in many cases with a synchronous proliferation of the connective tissue and the endosteum of the epiphyseal marrow directly below the joint cartilage"; and further: "The proliferation and extension over the surface of the cartilage of the synovial membrane is the earliest and most marked feature of these joints. The pannus may be composed of a very vascular granulation tissue infiltrated with lymphoid and plasma cells, with comparatively little intercellular material or may be a very dense fibrous tissue with very few vessels and no obvious infiltration." Of the periarticular and capsular tissues they state: "In all cases of proliferative arthritis changes occur in the capsule, usually synchronous with changes in the synovial membrane. This change consists in a proliferation of the connective tissue of the capsule and leads to a greater or less thickening usually of the entire capsule." They note that in the early stages, there may be a connective tissue with little intercellular substance which later becomes denser with more or less hyalinization and vascular obliteration. In both stages the tissue may or may not be infiltrated with lymphoid and plasma cells. Fisher's observations are in essential agreement. In addition, he notes that in the more central parts of the articular cartilage one may often find shallow ulcers whose floor is formed by connective tissue

formed by metaplasia of the superficial cartilage cells. In the later stages of the disease the extreme fragility of the affected bones is noted. Llewellyn and Jones⁸ have suggested substitution of the term fibrositis for chronic rheumatism, because they consider the basic anatomic lesion is one of inflammatory overgrowth, or hyperplasia of the white fibrous connective tissue. They further point out that, in chronic articular rheumatism, the periarticular, subsynovial and ligamentous tissues are at times more often and more deeply affected by the morbid process than the synovial or bony elements. Emphasis is also placed upon the importance of muscular degenerations in the rheumatic syndrome. Klinge and Grzimek's¹ studies indicate the importance of the "fibrinoid" degeneration in this type of arthritis as well as in rheumatic fever. The essential identity of the anatomic lesion in the experimentally produced subcutaneous nodules and those of rheumatic fever and rheumatoid arthritis has been noted. Considerable significance is attached to the experimental occurrence of this lesion because of its unusual character. Many observers have stressed the bone atrophy accompanying rheumatoid arthritis. Indeed, this change formed the basis for the classification of the disease as atrophic arthritis by Goldthwait.⁹ Swaim¹⁰ has noted the atrophy of the whole bony system in this type of arthritis. Howitt and Christie¹¹ emphasize the importance of the general progressive skeletal atrophy which they find demonstrable, before the onset of joint changes.

SUMMARY OF THE PATHOLOGICAL SIMILARITIES BETWEEN SCORBUTIC AND RHEUMATOID ARTHRITIS

It will be seen that there are many pathologic similarities between the experimental scorbutic and rheumatoid types of arthritis. Features in common include synovial proliferation and connective tissue pannus formation. In the capsular and periarticular tissues, connective tissue overgrowth is seen in both conditions. The hyaline streaks of fibrin usually found in association with the connective tissue hyperplasia of scorbutic arthritis, appear to correspond with the "fibrinoid" degeneration, which Klinge finds to be a basic lesion in the rheumatic diseases. Retrogressive changes in the articular cartilage are observed in both scorbutic and rheumatoid arthritis. In a few instances, fibrous tissue transformation of the subarticular marrow, noted by Nichols and Richardson in proliferative arthritis, has been seen in the scorbutic joints. General skeletal atrophy, most marked at bone ends, is seen in both the experimental and clinical arthritis. Muscle atrophy and degeneration occur in both conditions. Finally, fibrous nodules develop beneath the skin in experimental animals, that are remarkably like the early subcutaneous nodules of rheumatoid arthritis. One microscopic feature commonly but not constantly observed in rheumatoid arthritis is the presence of focal collections of lymphocytes in and about the synovial tissues. This change has been seen in only a few instances in the scorbutic joints and has never been a prominent feature. It is possible that if a more chronic process were produced experimentally, this lesion might be observed.

DISCUSSION

Scattered reports have directed attention to joint disabilities in the presence of vitamin C deficiency. Jackson and Moore¹² noted the prominence of joint manifestations in guinea pigs fed an exclusively milk diet. Smith¹³ observed that the first manifestations of scurvy in guinea pigs are swollen and tender joints. The diet employed by her consisted of a paste made of alfalfa meal and wheat flour with whole oats and water given *ad lib.* Howe¹⁴ fed guinea pigs rolled oats and fat free milk supplemented with small amounts of carrot and lettuce. By regulating the intake of carrots and lettuce he maintained the animals in a deficient state for periods of three months to a year. His interest was primarily in dental degenerative changes, but he states: "The usual joint affections occur to a marked degree, and when this condition has been maintained for a long time and the animals are restored to a normal diet, it is found that the legs have become fixed in an abnormal position. This seems to us to be more like rheumatism and arthritis deformans than many experimental conditions that have been called such." Stiner,¹⁵ in a paper entitled "Experiments on Rheumatic Diseases in Animals," observed that young guinea pigs fed sterilized food (e.g., hay, turnips, oats) and various kinds of prepared milk, developed joint swelling, disability and deformity. He recognized the vitamin C deficiency of the diet but was also inclined to ascribe a direct noxious effect to the pasteurized milk. He was impressed by the general similarity of the manifestations in the animals to the manifestations of rheumatism in man. It will be recognized that the experimental diets employed by the investigators cited are probably deficient in other food factors than vitamin C, including salts and other vitamins, although the outstanding deficiency was certainly of vitamin C.

GENERAL CONSIDERATIONS

Many of the epidemiological factors, previously considered,¹⁶ which apply to rheumatic fever, pertain also to rheumatoid arthritis. The evidence indicating the existence of latent scurvy and the factors relating to storage and utilization of vitamin C are equally pertinent. The observations suggesting that the vitamin C requirement may be enhanced by achlorhydria would appear significant in view of the relatively high incidence of this factor in rheumatoid arthritis. The data cited, indicating the depleting effects of fatigue and certain infections on the organic stores of vitamin C, suggest auxiliary mechanisms that might precipitate a significant deficiency state.

The impaired peripheral circulation, emphasized by Pemberton and Osgood¹⁷ in rheumatoid arthritis, would appear explainable on the basis of vitamin C deficiency. The pathology of chronic scurvy is dependent, to a considerable extent, upon the impairment of the capillary wall and attendant circulatory inadequacies.

The importance of acute infections and of focal infection, emphasized

particularly by Cecil¹⁸ and his school, is not denied. Indeed, the experimental data strongly suggest that certain infection may accelerate and aggravate the scorbutic arthritis, and in some instances, it would appear that the deficiency may, by lowering the resistance of the joint tissues to circulating bacteria, favor their lodgement and the development of a truly infectious (purulent) arthritis. Milder infections might occur with less virulent organisms.

Howitt and Christie¹¹ direct attention to the prodromal symptoms frequently preceding the onset of rheumatoid arthritis. These include loss of appetite, tachycardia, fall in blood pressure, a slightly raised temperature, sweating of the hands and feet, dermatographia, tremor, nervousness, loss of weight, an extreme degree of fatigue, disability, and vague muscular pains. It would seem significant that many of these symptoms are characteristic of latent scurvy.

There is a definite tendency among students of the subject, to consider rheumatoid arthritis a general constitutional disease with joint manifestations as its most serious feature. This is clearly evidenced by the reports of the American Committee for the Control of Rheumatism¹⁹ and of the Committee of the British Medical Association²⁰ as well as by numerous individual studies. The general atrophic changes often encountered in rheumatoid arthritis, involving skin, hair, fingernails, muscles and bony skeleton, have been particularly noted by Swaim.²¹ Swollen, puffy, edematous gums are frequently seen in this disease. Swaim²¹ observes: "The gums are spongy and teeth decay easily. The mouth resembles that of a scurvy patient."

Many writers have stressed the importance of nutrition, notably Goldthwait,²² Burnett and Ober,²³ Howitt and Christie,¹¹ Irons,²⁴ Fletcher,²⁵ Pemberton,²⁶ Rowlands²⁷ and Hall.²⁸ The latter notes: "We are constantly seeing patients with severe arthritis, who for months or years have been eating inadequate or deficient diets. In such cases, the diet has been the depleting factor." Rowlands,²⁷ and Fletcher and Graham²⁹ have presented indirect evidence that vitamin B deficiency may operate in the etiology of rheumatoid arthritis. The evidence is based essentially upon the frequent observation of atony of the musculature of the colon. Fletcher and Graham gave patients high vitamin diets with particularly generous amounts of vitamin B and observed improved tone in the bowel and frequently much clinical benefit. It is not improbable that vitamin B deficient states do indirectly contribute to development of arthritis. Nutritional inadequacies are likely to be multiple. Vitamin B deficiency appears to act largely through limitation of the voluntary food consumption by impairment of appetite. In this way, an inadequate vitamin C intake might follow in its wake, particularly if the food selection did not include the richer sources of this factor.

Although it is not the primary purpose of this paper to report clinical studies of rheumatoid arthritis which are in progress,³⁰ certain general facts

have emerged which appear worthy of comment. In the first place, careful inquiry into dietary habits of persons suffering from this disease has indicated that a very considerable number have been on faulty diets, and in many instances, surprisingly low in vitamin C containing foods. Further, capillary resistance tests (an index of latent scurvy) have shown, in general, low levels, and with the institution of high vitamin C containing diets, these levels have risen. Several cases reported here exemplify these findings.

CASE REPORTS

Case 1. S. T. B., white male, aged 42. On January 15, 1934, the patient thought that he had sprained his right ankle. The next morning, he found his knees, elbows, wrists and ankles were stiff. The left knee was considerably swollen and the other joints less so. He entered the San Francisco Hospital, Febr. 10, 1934, showing moderate swelling and pain in wrists, knees and the right ankle. Study of his dietary habits revealed striking inadequacies for several years due to unemployment. Cracked oats, bread, coffee, beans and stews formed the bulk of his foods. Just preceding the onset of arthritis, the diet had been somewhat more generous but still low in vitamin C. More than usual physical work and exposure immediately preceded the onset of arthritis. Capillary resistance tests (Dalldorf method) gave low readings. The dental condition was extremely bad with reddened, edematous gums. The patient was given the routine hospital diet with a daily supplement of one quart of orange juice. Improvement was rapid and recovery complete without further therapy. Four months later, the patient was found to have remained asymptomatic. The capillary resistance level had returned to normal.

The presence of vitamin C deficiency here can hardly be doubted. In fact, it appears that the patient probably suffered a scorbutic arthritis which, however, was clinically considered to be an early, relatively acute, rheumatoid type of arthritis.

Case 2. C. H., white female, aged 42, entered University of California Clinic, January 1, 1934, with a complaint of pain and swelling of right foot and ankle for past eight months. At the onset, she had an attack of pleurisy. Transient pains appeared in her elbows and ankles. A few days later, the pain in the left ankle became very severe. At about the fourth week, the ankle was said to be of a bluish-red color. At the clinic, the ankle showed a diffuse hard swelling with a yellowish area of discoloration at the medial aspect. Roentgen-ray examination revealed marked atrophy of the bone about the ankle joint. The roentgen-ray diagnosis was acute infectious arthritis. Diet analysis by an experienced nutritionist revealed a low intake of vitamin B and what was considered a very low intake of vitamin C. The capillary resistance test showed a surprisingly low strength. The ankle was placed in good position in a light ambulatory splint, and the patient returned to her home with diet instructions to supply a very generous amount of vitamin C. One month later, excellent improvement in the condition of the ankle was noted. The capillary resistance showed a moderate but definite elevation. A report of recent date indicates little or no residual disability.

Case 3. A. H., white male, sailor, aged 45, entered U. C. Hospital, March 1, 1935, with a typical erythema multiforme and a mild arthritis, dating back two weeks. On entry, examination showed swelling of knees with excess fluid, and some limitation of movement in shoulder. Dietary inquiry revealed generous and apparently adequate food intake including vitamin C up to five months ago, when the patient lost his job as

a merchant sailor. Since that time, the patient had been on relief, receiving a small cash allowance. He prepared his own food. The caloric intake was relatively generous, but except for potato, practically no vitamin C-containing foods were consumed. He ate little or no fresh fruit or vegetables in this period. Capillary resistance tests were considered within normal limit. Oral hygiene was poor, and the gums were puffy, red and edematous. On March 3, 1935, the patient was started on daily doses of sodium ascorbate (250 mg.) intravenously. The following day, the left wrist was painful to movement, and there was thickening over the first metacarpal phalangeal articulation. The erythema showed evidence of clearing. March 7: Pain and swelling in knees were subsiding, and the wrist pain had gone. Progressive clinical improvement ensued, which has persisted to date, in spite of the fact that a suppurative inguinal lymphadenitis has developed. At the present, five weeks after entry, the skin is clear and patient is free of arthritis. The general condition is improved and gums appear firmer. The patient was given 7 daily doses of sodium ascorbate (250 mg. each) intravenously, then doses three times a week for three weeks, following which he was advised to eat vitamin C-containing foods.

Case 4. L. H. F., male, aged 34. This patient is one who had a chronic arthritis of the rheumatoid type with marked disability and deformity. A more or less progressive development dated back to an onset 16 years previously. Dietary habits indicated a moderately but not severely low intake of vitamins B and C-containing foods. Capillary resistance tests gave strikingly low readings. The gums were puffy, reddened and retracted. The arthritic disability consisted in stiffness, deformity and pain in hands, wrists, elbows, feet and ankles. The patient was instructed to take one pint of orange juice daily. He has been on this régime for 15 months. Gradually the capillary resistance has returned to a nearly normal level at present. Although improved, it was distinctly low six months after onset of dietary régime. Although he has had recurrent attacks of pain in one or more joints, the painful episodes are distinctly less frequent and less severe. The patient considers his general sense of well being and arthritic condition distinctly improved.

The writer does not wish to be guilty of the single-minded zeal warned against by Pemberton.²¹ Indeed, he is in complete sympathy with a broad, unbiased approach to the problem, and realizes that many factors, some known, others not, lie in the background. It is felt, however, that the evidence indicates that vitamin C deficiency may operate as an important factor in the etiology of some cases of rheumatoid arthritis, and that the concept is worthy of serious consideration.

SUMMARY AND CONCLUSIONS

Subacute or chronic vitamin C deficiency in the guinea pig produces an arthropathy with manifold similarities to rheumatoid arthritis. These include synovial proliferation, intra-articular pannus formation, periarticular fibrous tissue overgrowth, bone atrophy and subcutaneous nodules. In certain instances, superimposed infection accelerates and accentuates the pathological process. In this study, infection in the presence of adequate vitamin C nutrition failed to produce arthritis. Brief evidence is presented that vitamin C deficiency may, by producing a locus of diminished resistance, also operate as a predisposing factor in the etiology of truly infectious (suppurative) types of arthritis. The general atrophic changes found in rheumatoid arthritis involving bony skeleton, muscle and skin, are seen also in

chronic vitamin C deficiency. Evidence indicating the probable clinical importance of latent scurvy, and the depleting effect of fatigue and certain infections on the organic stores of vitamin C, is noted. Clinical data are cited that the nutritional habits are frequently imperfect preceding the onset and during the course of rheumatoid arthritis. Experimental, epidemiological and clinical evidences afford the basis for the concept presented, that vitamin C deficiency may operate as a factor in the etiology of some cases classified as rheumatoid arthritis.

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