SUBCUTANEOUS NODULES IN CHRONIC ARTHRITIS *

CLINICAL, PATHOLOGICAL AND BACTERIOLOGICAL STUDIES

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Nodules varying in size and consistence are commonly found in the loose connective tissue beneath the skin in individuals with acute rheumatic fever. These nodules have been seen repeatedly by different observers and have come to be looked upon as a characteristic clinical and pathological finding in this condition.

Hillier¹ in 1868 was one of the first to describe these lesions. Meynet² in 1875 first pointed out that they bore a direct relation to acute rheumatic fever. Coates and Coombs³ considered subcutaneous nodules the most specific manifestation of rheumatic fever.

Not many observations have been reported concerning the frequency and structure of subcutaneous nodules seen in chronic arthritis. Hawthorne⁴ described subcutaneous nodules in six patients and considered rheumatic fever and rheumatoid arthritis different manifestations of the same process. Garrod⁵ also observed subcutaneous nodules in chronic arthritis. Wick⁶ saw a relation between the nodules found in chronic arthritis and those seen in acute rheumatic fever. Subcutaneous nodules in cases of chronic arthritis were also described by Coates and Coombs, Freund,⁷ and Dawson and Boots.⁸

If it should be shown that subcutaneous nodules are found as frequently in chronic arthritis as in acute rheumatic fever, and that the structure and etiology of the nodules in the two diseases are similar, important data would be supplied concerning the etiology of chronic arthritis. Help might also be obtained toward classifying the chronic arthritides from the etiological standpoint.

The object of this paper was to study the frequency, structure and bacteriology of subcutaneous nodules seen in chronic arthritis,

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and to compare these nodules with those occurring in acute rheumatic fever.

CLINICAL DATA

Material and Method: The patients studied were, for the most part, those who during the past year came to the outpatient department of the Medical School at the University of Minnesota for treatment of chronic arthritis. Subcutaneous nodules were carefully sought in 200 consecutive patients with chronic arthritis. The nodules were studied in respect to frequency, location, size, shape, consistence, development and duration. Nodules from twenty patients were removed and examined grossly. They were then cut into two or more parts under sterile conditions. A portion was fixed for microscopic study and another portion was cultured for bacterial growth. The histological structure of subcutaneous nodules found in chronic arthritis was compared with the structure of nodules of acute rheumatic origin and with experimental streptococcic nodules from rabbits.

Frequency: Dawson and Boots stated that the incidence of subcutaneous nodules in the 200 cases of "rheumatoid" arthritis examined by them was about 20 per cent. They believed that this might be higher than the general average, inasmuch as patients with subcutaneous nodules were sent to them because of their known interest in these lesions. Cecil⁹ referred to them as being present in from 3 to 4 per cent of the cases.

In our series of 200 patients with chronic arthritis, subcutaneous nodules were found in fifty-nine (29.5 per cent). We have not attempted to determine the relative frequency of the nodules in the different classes of non-specific chronic arthritis, since we have not been able to group our arthritic patients satisfactorily into different distinct classes such as rheumatoid arthritis (atrophic, proliferative), and osteo-arthritis (hypertrophic, degenerative). Forty-eight of the fifty-nine individuals with nodules were 50 years of age or older. Some of these cases presenting definite nodules would be classified by many as osteo-arthritis (hypertrophic, degenerative). The following history illustrates such a case:

Mrs. F. P., aged 75 years, complained for the past five years of joint pains involving the toes, ankles, knee, right hip, fingers, wrists and cervical spines. The onset of illness was gradual, with moderate pain and stiffness in multiple joints. A definite nodule 1 cm. in diameter was found overlying the ulna 2 inches

below the olecranon process. This nodule showed microscopically a structure similar to that found in other cases of chronic arthritis and acute rheumatic fever. The X-ray report of the right knee, right wrist, fingers, ankles, toes and cervical spines was "hypertrophic arthritis" in all except the ankles, which showed no change.

The individuals with nodules did not fall into any definite group and could not be distinguished in any way from a large number of arthritics without nodules.

Symptoms: The patients were frequently unaware of the presence of the nodules. In a few instances there was slight pain at times, especially in the nodules over the elbows when they were traumatized. Three persons having nodules on the plantar surface of the foot complained of pain in the location of the nodule and walked with a decided limp, which was definitely relieved after the nodules were removed. In one person a large nodule on the dorsum of the hand caused difficulty in extending the fingers.

Duration: In most cases it was difficult to determine the duration of disease since the patients had not known of the presence of the nodules. In a number of persons the nodules were known to have been present from a few months to as long as fifteen years. A few individuals described what appeared to have been nodules, which spontaneously disappeared after having been present from a few months to a few years.

Distribution: The nodules in this series were found chiefly on the extremities. They were not searched for as carefully on the trunk and spine in all individuals. There would seem to be no reason why nodules might not occur in such locations. Two patients had nodules in bilateral arrangement over the sacro-iliac joints. Nodules frequently occurred bilaterally in the same location, especially over and below the elbows. In one individual there were nodules similar in size over the dorsum of each hand. These nodules were attached to the lower surfaces of the tendons running to the little fingers. In another person nodules of the same size were found on the dorso-lateral surfaces of both feet, just behind the little toes. Twenty-four of the fifty-nine patients had a more or less symmetrical bilateral distribution of the nodules. This was especially true over the elbows.

Nodules were frequently multiple in the same location, especially over the olecranon processes, about the finger joints and over the tibias. They were found much more frequently on the upper ex-

tremities than on the lower. In fifty-nine patients nodules were found in seventy-seven locations (excluding bilateral symmetrical occurrences). Sixty-three of these locations were on the upper extremities, twelve on the lower extremities and two over the sacro-iliac joints. The distribution was as follows:

	Location	Incidence
<i>Upper Extremities</i>		
	Olecranon processes.....	28
	Fingers (over joints)	13
	Below elbows	12
	Dorsum of hand.....	7
	Palmar surface of hand	2
	Fingers (dorsum and between joints).....	1
	Total	63
<i>Lower Extremities</i>		
	Tibia (upper half)	4
	Dorsum of foot	4
	Plantar surface of foot	2
	Knee (outer and lateral aspects).....	2
	Total	12
<i>Trunk</i>		
	Sacro-iliac joints	2

Gross Appearance: On clinical examination the nodules were found to vary in diameter from 5 mm. or less to 3 cm. (Figs. 1 and 2). Those occurring over the olecranon processes tended to be small and those located below the elbow were frequently large. On superficial examination all were movable and not attached to the skin, but some were fairly firmly attached to the underlying tissues. On palpation most of the larger nodules were cystic and in some of the cysts a number of firm, disconnected masses of tissue could be felt. These masses within the cysts were occasionally attached to tendons. This was especially true on the dorsum of the hand.

The nodules were generally easily removed. They often had a definite capsule but in some instances this was poorly defined. When sectioned and examined grossly, multiple areas of necrosis surrounded by fibrous tissue were usually seen. Necrotic and mucinous material could frequently be expressed from the center. In none of the cases did we find the nodules calcified, as reported by Wick.

The nodules were grossly not unlike those sometimes occurring with syphilis and referred to as juxta-articular nodules. Subcutaneous nodules in syphilitic patients coming to the outpatient department have been found to be rare.

MICROSCOPIC STRUCTURE OF NODULES

A comparative study was made of the structure of subcutaneous nodules seen in acute rheumatic fever, of nodules produced experimentally by injecting streptococci in small doses subcutaneously into rabbits, and of nodules found in individuals with chronic arthritis.

Subcutaneous Nodules in Acute Rheumatic Fever: Hirschsprung¹⁰ in 1881 gave the first microscopic description of subcutaneous nodules found in patients having acute rheumatic fever. The nodules which he studied consisted of different modifications of connective tissue cells which varied in size and shape. The cells were irregular and spindle-shaped, and contained one or more vesicular nuclei larger than those found in ordinary granulation tissue. There was a homogeneous ground substance between the cells. The number of blood vessels was increased. He considered the nodule a localized area of inflammation which had a tendency to undergo necrosis.

Barlow and Warner,¹¹ Swift,¹² and Clawson, Bell and Hartzell¹³ observed that the cellular reaction in a rheumatic subcutaneous nodule was similar to that found in the heart valves in acute rheumatic endocarditis. Cavafy¹⁴ called attention to the presence of proliferative endarteritis in the nodules from acute rheumatic fever. This endarteritis sometimes became extensive enough to close the lumen of the vessels entirely.

The subcutaneous nodules were found by Fitcher¹⁵ to consist of fibrous tissue in various stages of development, and the cellular element to be made up of small round cells, fibroblasts, polymorphonuclear leucocytes and giant cells. Some of the giant cells contained as many as twenty-six nuclei.

Frank¹⁶ observed peripheral and central zones in the nodules. The central area was a homogeneous mass which stained red with eosin. He decided that this homogeneous material was fibrin. The peripheral zone consisted partly of spindle cells and partly of epithelioid cells. There were numerous leucocytes. He noted variation

in structure in different nodules and considered this variation to be due to different stages of development. He considered the primary reaction in the nodule an exudate of polymorphonuclear leucocytes, which was followed by a wandering in of round cells and by a proliferation of the surrounding connective tissue.

Swift described the nodules as being made of a conglomerate number of smaller nodules. The cellular structure was similar to the structure of nodules found in the heart and other parts of the body. Clawson¹⁷ studied nodules of acute rheumatic fever histologically in serial sections. The nodules under low magnification give the impression of multiple confluent granulomas. They are composed of multiple inflammatory foci of similar structure. The inflammatory reaction is chiefly proliferative and polyblastic in type, *i. e.*, fibroblasts and polyblasts are the most conspicuous cellular elements. Many of the polyblasts are multinucleated. Some polymorphonuclear leucocytes are found and there are irregular areas of necrosis.

Experimental Streptococcic Subcutaneous Nodules: Areas of polyblastic inflammation were observed by Small¹⁸ in a papule developing at the site of an intradermal injection of a streptococcic vaccine.

In previous experiments, in a relatively high percentage of rabbits which had been injected intradermally and subcutaneously with strains of streptococci, Clawson¹⁹ produced small, nodular, polyblastic lesions that were similar in the character of the cellular reaction to the subcutaneous nodules found in rheumatic inflammation in man.

Workers who have studied the subcutaneous nodules agree that the nodules consist of proliferating connective tissue cells and a cellular exudate of lymphocytes, plasma cells and polymorphonuclear leucocytes in varying numbers. In the center of most of the nodules there is some necrosis.

Subcutaneous Nodules in Chronic Arthritis: There have not been many microscopic examinations of subcutaneous nodules of chronic arthritic origin. Wick studied the histological structure of subcutaneous nodules from chronic arthritis and acute rheumatic fever, and found a marked similarity in the two conditions. Coates and Coombs compared the histological structure of nodules from acute rheumatic fever, from chronic rheumatoid arthritis, from Still's disease, and from a case of subacute bacterial endocarditis. They decided that the structure of the nodules in these conditions was

closely related, if not identical. Freund also gave a description of the microscopic structure of nodules in cases of chronic arthritis and discussed the relation between rheumatic fever and rheumatoid arthritis. Dawson and Boots observed in their fourteen cases of rheumatoid arthritis areas of central necrosis, which they thought were due to a gelatinous swelling and disintegration of collagenous bundles. They found this necrosis to be more extensive than that found in the nodules of acute rheumatic fever. They also found fibrin and an inflammatory cell infiltration in the areas of central necrosis in some instances. Large mononuclear cells were situated around the necrotic centers, generally in a radial arrangement. They considered these cells and their arrangement to be responsible for the characteristic appearance of the lesions. The blood vessels showed subendothelial deposits of fibrin, hyperplasia of the subendothelial cells with narrowing of the lumen, and perivascular cell infiltration by large and small round cells.

We have examined microscopically subcutaneous nodules removed from twenty cases of chronic arthritis. The structure in general is similar to that described by Dawson and Boots and others.

The nodules removed are found in most instances to be made up of multiple inflammatory areas (Fig. 3). The centers of these areas commonly show varying stages of necrosis (Fig. 4). In the smaller nodules only necrotic nuclear changes such as pyknosis and karyorrhexis are most commonly seen. In the larger nodular, necrotic areas the cellular structure has disappeared. Two types of structure are seen in the necrotic centers, a hyaline, eosin-staining material and a fibrillar substance that stains with hematoxylin. Scattered in this necrotic material are varying numbers of polymorphonuclear leucocytes. Surrounding the necrotic centers there are many mononuclear and multinucleated cells (polyblasts). These vary in size and shape. Many of them resemble the epithelioid cells in a tuberculous lesion. These polyblasts generally, but not always, have a marked tendency to be arranged in a radial or palisade fashion (Figs. 5 and 6). In this respect the arrangement is similar to that so commonly found in the heart valve in acute rheumatic endocarditis. A hyalinized material, similar to that seen in the valve in acute rheumatic endocarditis, is often seen (Fig. 3). Scattered among the larger and irregularly shaped polyblasts are small polyblasts. Polymorphonuclear leucocytes are scattered among the polyblasts, in many cases in small

pockets or abscesses. The nodules in these cases of chronic arthritis simulate abscesses more closely than the acute rheumatic nodules which we have studied. These necrotic, abscessed areas, since they contain streptococci, would probably tend to bring about a state of hypersensitiveness to streptococci in the patient. The small blood vessels in practically all cases show a marked perivascular increase in polyblasts, polymorphonuclear leucocytes and small lymphocytes. In some vessels the walls are thickened and the endothelium has swollen to the extent of almost obstructing the lumen. Depending apparently upon the age of the nodules, there are in most instances varying degrees of fibrosis around and about the smaller, nodular, granulomatous or necrotic areas.

The structure of the nodules from chronic arthritis does not differ in any respect, except degree, from that described in the nodules in the subcutaneous tissues, joints, tendons, galea aponeurotica, diaphragm, tongue, tonsils, arteries, heart valves, and auricles and ventricles of the heart in acute rheumatic fever. It is the structure so commonly found in acute rheumatic fever, or in nodules produced experimentally in animals by injecting streptococci. The cellular reaction in the three conditions seems probably to be due to the same cause. This type of cellular reaction is found in other streptococcic infections. The necrotic and cellular reactions and the vascular changes can be produced experimentally in rabbits and monkeys by injecting streptococci of low virulence in small numbers. The fact that subcutaneous nodules structurally similar to subcutaneous nodules in acute rheumatic fever are found in so high a percentage of cases of chronic arthritis strongly suggests a common etiology, at least in most cases.

BACTERIOLOGY OF SUBCUTANEOUS NODULES

Diplococci were demonstrated in smears from acute rheumatic subcutaneous nodules by Poynton and Paine.²⁰ Costa²¹ was able to culture streptococci from rheumatic nodules. Irish²² obtained material from rheumatic subcutaneous nodules by puncturing them with a needle. Of the six cases examined by this method he obtained streptococci in three. Swift,²³ in describing reactions produced in rabbits by injecting streptococci, referred to strains isolated from subcutaneous nodules from acute rheumatic fever. Leichtentritt²⁴ found streptococci in one of three nodules cultured.

Previous to this report we attempted to culture bacteria from three subcutaneous nodules of rheumatic origin, but failed to obtain growth. Billings, Coleman, and Hibbs,²⁵ found *Streptococcus viridans* in a "fibroid nodule" from a patient with chronic arthritis. The location of the nodule was not given in their report. Aside from this report, no positive cultures from subcutaneous nodules in chronic arthritis have been reported. Wick was not able to obtain organisms from the nodule which he cultured. Dawson and Boots cultured nodules from fourteen patients with chronic arthritis, but had negative findings in all cultures.

We removed the nodules under sterile conditions from twenty of our patients. Seventeen of these were cultured. The nodules were brought to the laboratory immediately in sterile test tubes. They were then placed in sterile Petri dishes and cut into parts with sterile scissors. The part to be cultured was further macerated by cutting it several times with the scissors. The macerated material was then placed in a test tube containing about 10 cc. of beef infusion broth, which was similar to that used for culturing the blood from patients with acute rheumatic fever and chronic arthritis. This broth had a reaction of pH 7.6 and contained 0.2 per cent of dextrose. The material in the broth was incubated at 37° C and examined by smear preparation about three times a week. Growth, when present, occurred as a rule in less time than in blood cultures; however, cultures were not discarded until they had been incubated for at least one month. Of the seventeen nodules from different patients cultured by this method streptococci were recovered in twelve (70.6 per cent). *Staphylococcus albus* was obtained from one. Some of the strains grew well and some grew poorly. Morphologically the strains as a rule were diplococci, though two strains grew out into chains of diplococci. All were Gram-positive and produced green discoloration faintly when grown on a sheep blood agar plate for twenty-four hours at 37° C.

SUMMARY AND DISCUSSION

Two hundred patients having chronic arthritis were studied to determine the frequency of subcutaneous nodules in this disease. Nodules varying in diameter from 5 mm. to 3 cm., and in number from one to several per patient, were found in 29.5 per cent of the cases.

Structurally these nodules seemed to be similar to those found in acute rheumatic fever and to those produced in animals by injecting streptococci. They tended to be larger in chronic arthritis. The microscopic structure was chiefly polyblastic in character, but small areas of necrosis and abscess formation were commonly seen.

When these nodules were macerated under sterile conditions and cultured in beef infusion dextrose broth, diplococci morphologically and culturally similar to those commonly found in the blood of patients having acute rheumatic fever or chronic arthritis were isolated in 70.6 per cent of the cases.

The frequency of the subcutaneous nodules in acute rheumatic fever and chronic arthritis, the similarity of the gross and microscopic structure of the nodules in these two conditions and in experimental streptococcic nodules, and the frequency with which streptococci can be cultured from the blood in acute rheumatic fever and from the blood and nodules in chronic arthritis, strongly suggest that acute rheumatic fever and chronic arthritis for the most part have a common streptococcic etiology and that the two diseases are in all probability different manifestations of the same process.

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DESCRIPTION OF PLATES

PLATE 46

FIG. 1. Subcutaneous nodule on arm below elbow.

FIG. 2. Large subcutaneous nodule on right side of foot.

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PLATE 47

- FIG. 3. A small subcutaneous nodule and part of a larger one lying near each other. The smaller nodule shows a hyalinized material and cellular content similar to that in a valve in acute rheumatic endocarditis.
- FIG. 4. A nodule showing a necrotic center with radial arrangement of polyblasts around the necrotic area.
- FIG. 5. Cellular content of a nodule against the necrotic center on the right.
- FIG. 6. Palisade arrangement of cells against the necrotic center in the nodule.

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