

EXPERIMENTAL SUBCUTANEOUS RHEUMATIC NODULES*

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The subcutaneous rheumatic nodule is a localized area of inflammation, mostly proliferative in character, found in the loose connective tissue beneath the skin in a limited number of cases of acute rheumatic fever. Its structure is similar to that found in the Aschoff nodule in the heart or in rheumatic inflammation in other parts of the body, as in the joints, galea aponeurotica, diaphragm, blood vessels, etc.

Apparently the first written account of these subcutaneous nodules was given by Hillier¹ in 1868. In 1875 Meynet² pointed out that these nodular areas bore a direct relationship to rheumatic fever. The nodules, according to Angel Money,³ are less likely to occur in the extremely acute cases than in the chronic. Cheadle⁴ seldom found them in acute rheumatic fever except in childhood.

Hirschsprung⁵ in 1881 gave the first microscopic description of the nodules. He described them as consisting of connective tissue cells in different modifications. These cells varied in size and shape. Some were spindle-shaped and others were irregular. They contained one or more vesicular nuclei. These nuclei, he observed, were larger than those found in ordinary granulation tissue. He also noted that the ground substance between the cells consisted of a homogeneous material and that there was an increase in the number of blood vessels. In structure, the nodule resembled the tubercle, he thought, but did not have its typical appearance. He defined the nodule as being a localized area of inflammation with a tendency to undergo necrosis.

In 1881 Barlow and Warner⁶ described the reaction in these subcutaneous rheumatic nodules as being similar to the reaction in the valves in acute rheumatic endocarditis. The same observation has recently been made by Swift.⁷

The presence of a proliferative endarteritis in these nodules was observed by Cavafy⁸ in 1883. He noticed that the proliferating intima completely closed the vessel in some cases.

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Futcher⁹ in his microscopic description of the subcutaneous rheumatic nodule states that it consists of fibrous tissue in various stages of development. In some nodules he found the cellular element to be made up of small round cells, fibroblasts, and polymorphonuclear leucocytes. He also noted giant cells, some of which contained as many as twenty-six nuclei. All stages were present from the young cellular nodules to the older fibrous ones. Some nodules even became calcified.

The most complete microscopic description of the subcutaneous rheumatic nodules was made by Frank¹⁰ in 1912. He described them as being divided into a central and a peripheral portion. The center consisted of a homogeneous mass which stained intensely red with eosin, and by special staining he decided that this homogeneous material was fibrin. This fibrinous exudate extended out between the cells into the periphery. The periphery consisted of proliferative connective tissue which appeared partly as spindle cells and partly as epithelioid cells. Scattered among the proliferating cells a large number of leucocytes could often be seen. A variation in structure was noted in different nodules. This variation Frank considered to be due to different stages in the development of the same process, and he thought the primary reaction in the nodule was an exudation of polymorphonuclear leucocytes which was followed by a wandering in of round cells and by a proliferation of the surrounding connective tissue cells.

Swift⁷ described the subcutaneous nodules as being made up of a conglomerate number of smaller nodules and as being similar in structure to the nodules found in the heart and other parts of the body. He observed that the center consisted of necrotic material and a small amount of fibrin.

There seems to be a general agreement by observers who have studied the subcutaneous rheumatic nodules that they consist of proliferating connective tissue cells and a cellular exudate of lymphocytes, plasma cells, and polymorphonuclear leucocytes in varying numbers and that in the center of most of the nodules there is a greater or less amount of homogeneous substance consisting of necrotic material and fibrin. There is also agreement that anatomically and etiologically the subcutaneous nodule is similar to the nodule in the heart described by Aschoff,¹¹ Geipel,¹² Coombs,¹³ and others, and to the type of inflammation found in other parts of the

body in acute rheumatic fever. This type of inflammation has come to be considered by many observers a specific reaction to the rheumatic virus.

In this paper a microscopic study is made of human subcutaneous rheumatic nodules and of the nodules produced experimentally in the subcutaneous tissue in rabbits by injecting streptococci. The purpose is to compare the structure of a known rheumatic lesion with that of a lesion which has been produced experimentally to arrive at further conclusions concerning the causal relation of streptococci to rheumatic infections.

HUMAN SUBCUTANEOUS RHEUMATIC NODULES

The human subcutaneous rheumatic nodule which is studied in this paper was removed from the subcutaneous tissue of a patient having acute rheumatic fever. The nodule was found, upon microscopic examination of serial sections of the entire nodule, to be made up of many smaller nodular areas of inflammation. The reaction observed in this nodule was chiefly proliferative in character, but in many parts exudates of polymorphonuclear leucocytes, lymphocytes, and what appeared to be fibrin were noted (Fig. 1). The proliferative cells varied in size, shape and in staining qualities. Some of the nuclei were vesicular in character and some were hyperchromatic. The cytoplasm also varied in its degree of taking the basic stains. Many of these cells were multinucleated. Some of the nodular areas showed more or less necrosis in the centers. There was an increase in the number of blood vessels, and proliferative endarteritis was noticed in the smaller vessels. Morphologically the reaction observed in this nodule was similar to that described by Hirschsprung, Fitcher, Frank and others.

EXPERIMENTAL SUBCUTANEOUS RHEUMATIC NODULES

Nodules were produced in the subcutaneous tissues of rabbits by injecting different strains of streptococci in varying amounts and at different intervals. These nodules were removed and the microscopic structure was studied and compared with the structure of the human subcutaneous rheumatic nodule.

Five different strains of streptococci were used in the experiments. Two of these strains were isolated from the blood of patients having

acute rheumatic fever, one from the blood of a patient with subacute bacterial endocarditis, and two from pus from sinuses in cases of sinusitis. All of these organisms produced methemoglobin on the blood agar plate. Those strains isolated from the blood of patients with acute rheumatic or subacute bacterial endocarditis were less virulent to rabbits than the strains isolated from the sinuses.

Ten rabbits were injected intracutaneously and subcutaneously in many places with these organisms. Most of the animals had been previously injected with strains of streptococci intra-arterially through the left ventricle of the heart. Others had been previously injected subcutaneously in one area with a mixture of streptococci and agar. Just what part allergy may have played in the reaction in these experiments cannot be stated definitely.

The reaction found in the injected areas of the animals depended upon the virulence of the organism, the number of organisms injected, and the time of removal of the nodules after injection. The most virulent organisms tended to produce abscesses but in some cases typical proliferative nodules were produced. With the same organism the reaction varied according to the number of organisms injected. With a very few organisms proliferative nodules were produced, while with larger amounts abscesses resulted. With the same organism and approximately the same dose the nodules examined a day or two following the injection, as a rule, showed chiefly polymorphonuclear leucocytes, while in the nodules examined at from seven to fifteen days after the injection the chief reaction was proliferative in character. These findings are in agreement with Frank's conception of the pathogenesis of subcutaneous nodules, *i.e.*, the first reaction is an exudative one which is followed by a wandering in of lymphocytes and by a proliferation of the connective tissue cells. In all the rabbits injected some proliferative nodules were found, but such nodules were most frequent in the rabbits injected with small doses of the less virulent organisms. With the more virulent organisms there was a greater tendency for abscesses to develop.

In the proliferating nodules produced in rabbits many mononuclear and multinucleated cells with vesicular nuclei were observed (Figs. 2, 3 and 4). Some cells were large and irregular. Morphologically the cells found in these nodules appear similar to those in the human rheumatic subcutaneous nodules and in the human

Aschoff nodules in the heart. In some of these nodules, areas of slight necrosis were noticed. A varying number of polymorphonuclear leucocytes and lymphocytes were also present. There was an increase in the number of blood vessels and in some of these nodules there was an endarteritis.

It seems evident from these experiments that, by injecting streptococci into the subcutaneous tissues of rabbits, lesions can be produced which are morphologically similar to the nodules found in the subcutaneous tissue in cases of acute rheumatic fever. Since these experimental nodules occur obviously as a result of injecting streptococci, the probable conclusion is suggested that acute rheumatic fever and the type of inflammation associated with it are of streptococcal origin.

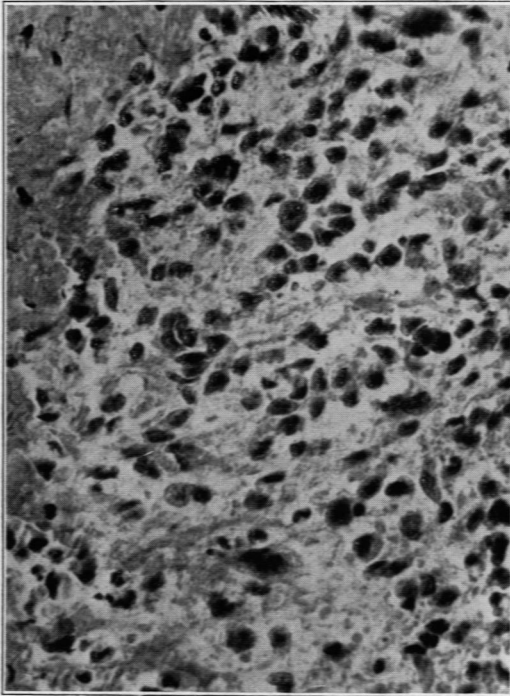
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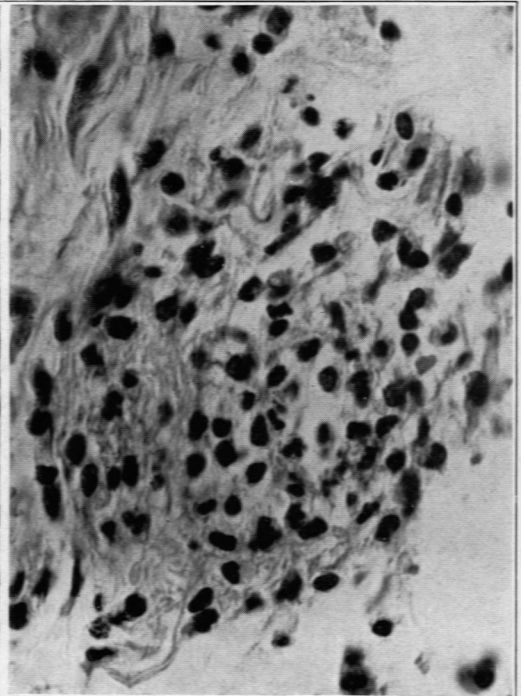
DESCRIPTION OF PLATE

PLATE 130

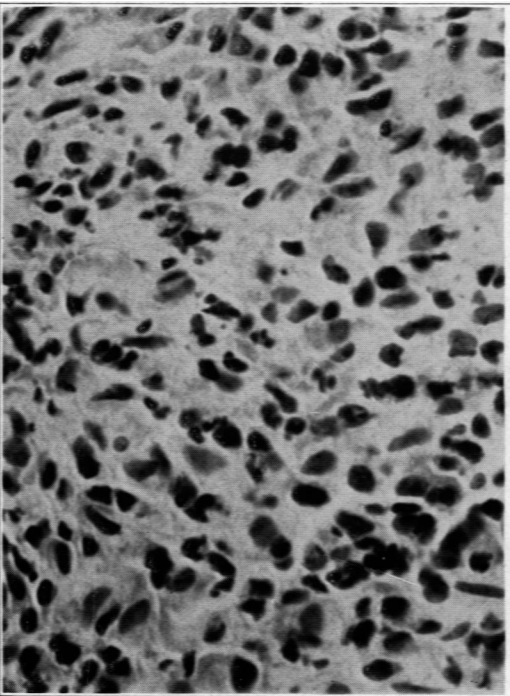
- FIG. 1. Human subcutaneous rheumatic nodule.
- FIG. 2. Experimental nodule in the subcutaneous tissue of a rabbit.
- FIG. 3. Experimental nodule in rabbit showing irregular proliferative cells.
- FIG. 4. Experimental nodule in rabbit showing mononuclear and multinucleated proliferative cells.



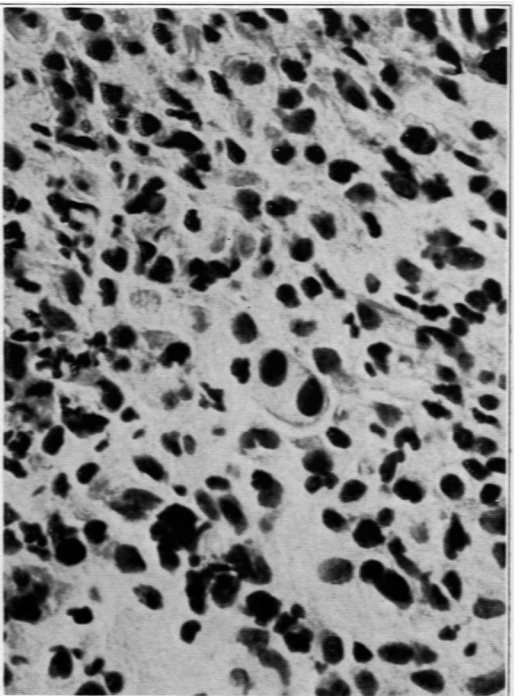
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