Section of Balneology and Climatology.

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Tissue Reaction in Disorders of the Rheumatic Group: with particular reference to Subcutaneous Nodules.

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This paper is proffered as another link in the chain of evidence which is tending to establish the relation of orthodox rheumatic infection to multiple infective arthritis of unknown origin. This relationship is thought to be such that both these disorders are but varied expressions of the same disease; circumstance, organ inferiority, and immunity deciding the site of election and the exuberance of the reaction.

Before proceeding further it is only reasonable to offer a short explanation as to why all types of non-specific polyarthritis are grouped together as a whole. Until recent date it was the custom to do this in Great Britain, and in America it is the rule rather than the exception to divide multiple non-specific, non-suppurative arthritis into atrophic and hypertrophic categories. Though it is good practice to recognize different clinical types and not difficult to demonstrate the outstanding difference between a fully established "atrophic" case—with its profound metabolic disturbance, symmetrical fusiform polyarthritis, enlarged spleen and glands, achlorhydria and anæmia without discoverable foci of infection—and a mild case with little or no systemic disturbance, arthritis of scattered distribution, absence of gross dislocation of the homopoietic mechanism and obviously septic teeth, yet it is another affair to decide exactly where the so-called "atrophic" or "true rheumatoid" case ends and other forms begin, when, say, twenty-five cases are seen side by side, each displaying only a degree less disability than the last. Again, the aspects of disease change from time to time. The so-called "atrophic" case of to-day is the less advanced case of to-morrow, and vice versa. And this is only to be expected, for what two individuals show the same systemic or local disturbance in any given infection? Would not either every case of rheumatic fever develop mitral stenosis, or else this complication remain unknown? It would be good policy to visualize the clinical types of arthritis under review as being "severe," "moderately severe," or "formes frustes."

The reasonableness of allying orthodox to heterodox rheumatic infection is based upon two main principles. In general, the well recognized fact that many disorders of an infective nature are prone to exhibit widely divergent manifestations: in particular, the merging of one condition into the other, the occurrence of common symptoms, complications and cardinal signs. Syphilis, with its protean and ubiquitous attack upon joints, bones, viscera and nervous system, may be instanced

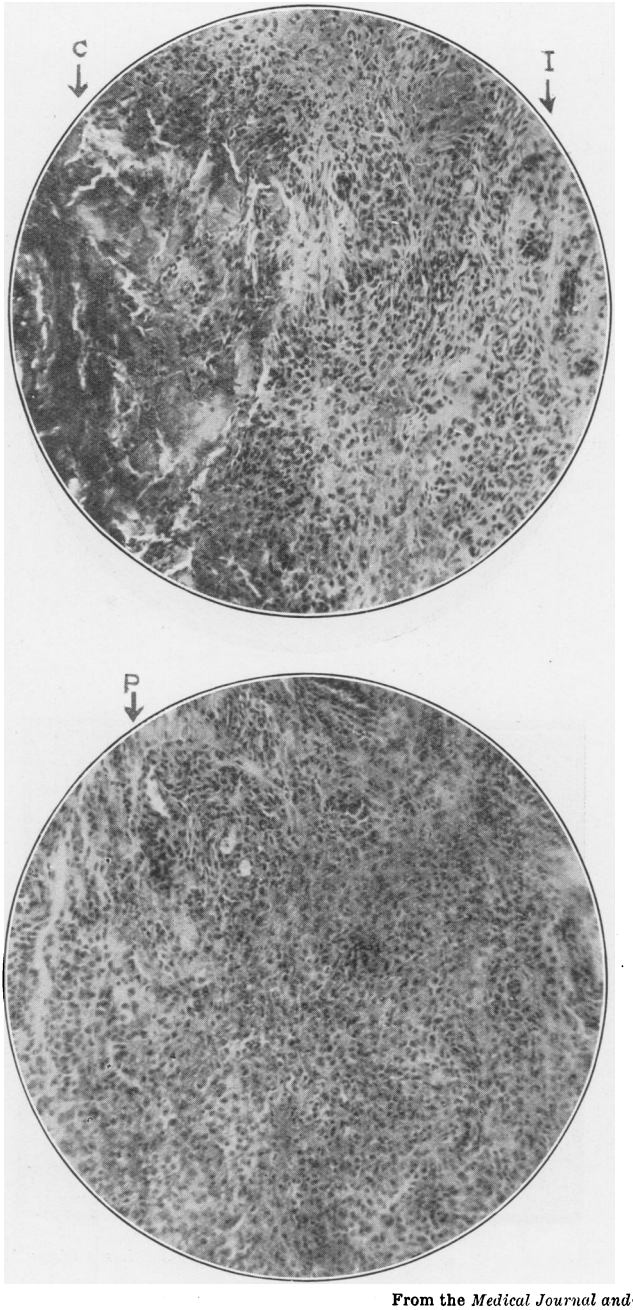
as an example of the first principle, and the familial [1] and personal history of rheumatic fever, the subcutaneous nodules and carditis of orthodox type in cases of infective arthritis, as an example of the second.

How then does tissue reaction help to consolidate or refute the suggestion that orthodox and heterodox infection are related?

It is now an established custom to diagnose certain types of disease by histological examination, even after failure to incriminate known or unknown organisms. Thus a lesion can be estimated as being syphilitic or tuberculous, and not infrequently such widely differing conditions as lymphadenoma, gonorrhœal salpingitis and amœbic colitis can be correctly diagnosed by their histological patterns. It is proposed therefore to reorganize the pathological data available in such a manner as to present what is claimed to be a reaction specific, not only for orthodox, but also for heterodox rheumatic infection.

(1) *The stages by which the conclusion has been reached that orthodox rheumatic infection gives a specific tissue reaction.*

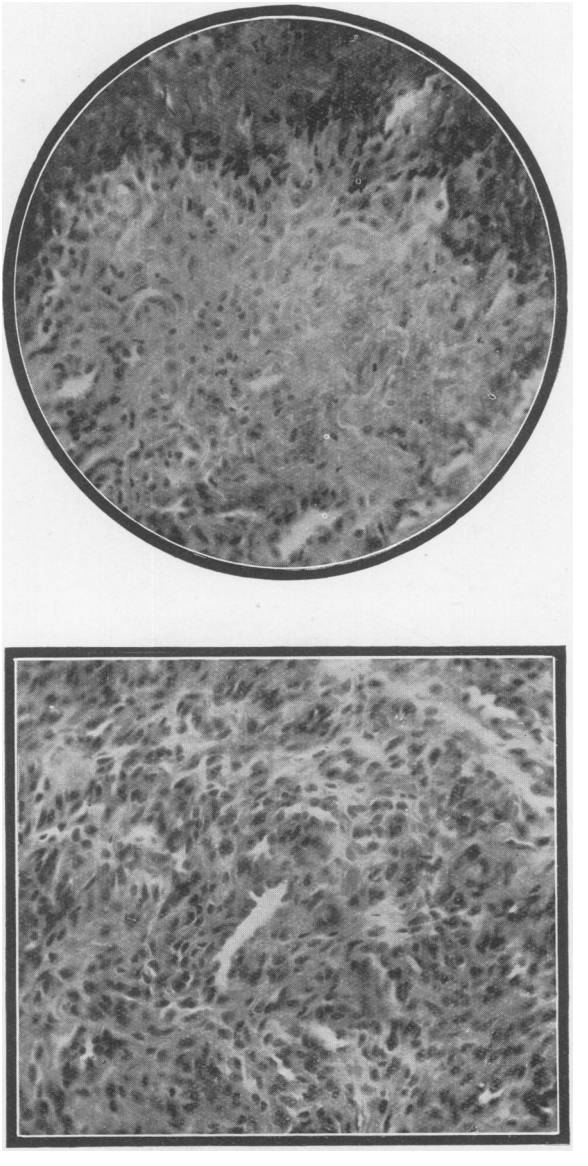
Sauvages [2] in the second half of the eighteenth century, is stated to have been the first to describe subcutaneous nodules, but Froriep [3] is probably actually the first observer who associated these with rheumatic disorders. Though various other writers, prior to 1881, described subcutaneous nodules, it is to Barlow [4] and Warner that we owe not only the classical description, but the statement that "Such nodules belong strictly to the fibrous tissues, and in nature are probably homologous with the inflammatory exudate which forms the basis of a vegetation on a cardiac valve." The discovery of the submiliary nodule in the rheumatic myocardium by Geipel [5] in 1905 and by Aschoff [6] in 1906 was the next important discovery, though Poynton and Still [7] in 1899 had drawn attention to the inflamed areas in the serous membranes of active rheumatic carditis. In 1911 Carey Coombs [8] was able to point out that the histological elements of the subcutaneous nodule, the submiliary nodule, the serous membranes of the heart and the synovial membrane of joints affected by rheumatic fever were identical. In 1925 Coates [9] described subcutaneous millet-seed granules in subacute rheumatic children which histologically were pocket editions of the subcutaneous nodule and probably homologous with the submiliary cardiac nodule. Coombs [10] has advanced the hypothesis of blood-borne streptococcal infection by showing histologically the manner in which the heart is attacked. In brief his contention is as follows: Streptococci of "parvenu pathogenicity," akin to those normally found in the alimentary tract are disseminated in the blood-stream and develop a special affinity for the cardiac muscle. A specific reaction follows, the stages in which are vascular thrombosis, endothelial response and a new vascular canalization. A fibrotic zone then surrounds the submiliary nodule so formed and the centre of this becomes destructuralized, with the eventual formation of a scar of dense fibrotic tissue. This process spreads by the newly formed vascular tissue, right up to the base of the valve flap, which in its turn becomes canalized, so that if the inflammatory process comes to lie under the free edge of the flap, the endothelial lining at the point of contact with its opposite number is liable to rupture, with the formation of a cap of protective fibrin and thus the basis of a cardiac vegetation is formed. Describing the histology of rheumatic infection, Coombs [11] says "the centre of the lesion is a thrombosis around which is a zone of extraordinarily rich and exuberant proliferation of fibrous and endothelial cells; these last throwing off not only detached uninucleate cells, but also new capillary buds in great numbers, and forming, possibly as an early phase of this budding, the multinucleate cells that are so striking a feature of the rheumatic reaction. These characters, the thrombotic centre and the endothelial periphery, stamp the node as a vascular lesion."



From the *Medical Journal and Record*)

FIG. 1.—RHEUMATIC FEVER.

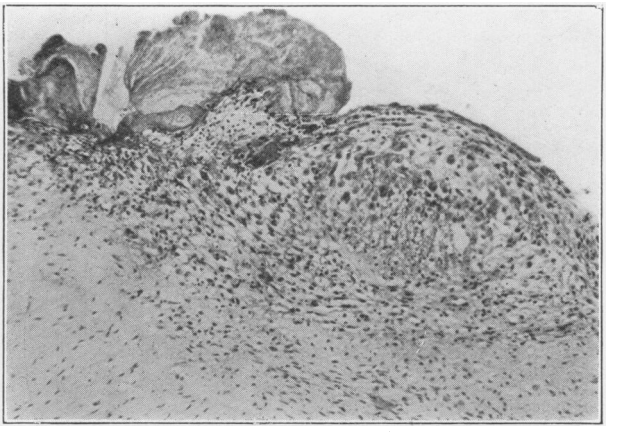
Subcutaneous node. Sections of a relatively large lesion arising during the acute stage of the disease in a child. The lesion is in a fairly early phase. A mass of autolysing fibrin occupies the centre (C). The intermediate zone is composed of inflammatory cells (I); the peripheral zone, of granulation tissue in which at a later stage large numbers of young capillaries arise (P).



(From the *Archives of Disease in Childhood*)

FIG. 2.—RHEUMATIC FEVER.

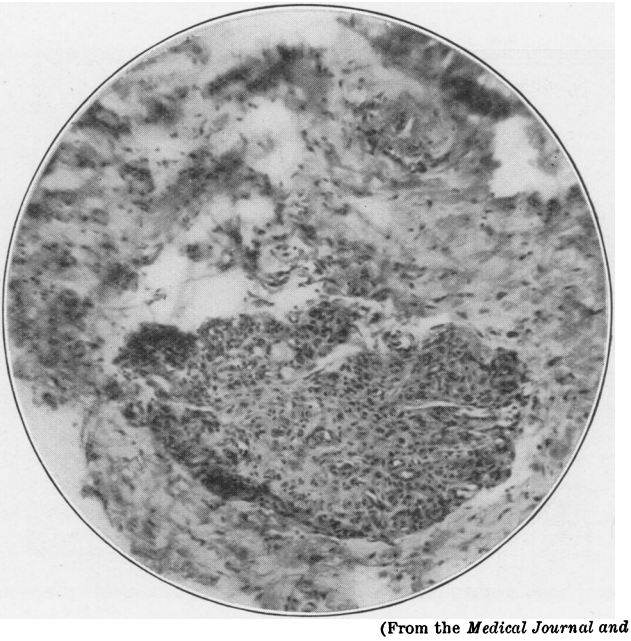
Subcutaneous node. A higher power view of a rheumatic node in its early stages showing exuberant production of new fibrous and vascular tissue.



(From the *Medical Journal and Record*)

FIG. 3.—RHEUMATIC FEVER.

Valvular endocardium. Section of "vegetation" of acute rheumatic endocarditis. A nodule of inflammatory cells lies beneath the valvular endocardium. Its histological characters are essentially those of the nodule found in the myocardium and mural endocardium. At one point the stretched endothelial lining has ruptured and a protective mass of fibrin lies over the rupture.



(From the *Medical Journal and Record*)

FIG. 4.—SUBACUTE RHEUMATIC INFECTION.

Millet seed granule. From a child without signs of organic cardiac disease. The lesion, only just palpable, has, in miniature, all the characters of the larger lesions found during the acute phase of frank rheumatic fever. It is sharply circumscribed and is rich in newly formed capillaries.

(From the *Archives of Disease in Childhood*)

FIG. 5.—SUBACUTE RHEUMATIC INFECTION.

Millet seed granule. Higher power. Note the formation of new capillaries.

(2) *The stages by which the conclusion is reached that heterodox rheumatic infection gives a similar tissue reaction to that of orthodox infection.*

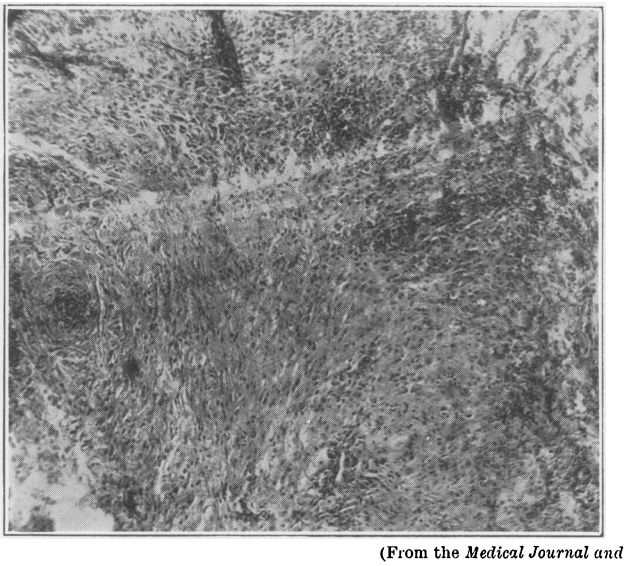
Hawthorne [12] in a particularly well-written monograph stated that "it is to Heberden (1710-1801) and Haygarth (1740-1827) that the responsibility of first endeavouring to advance rheumatoid arthritis to the position of an independent disease must be attached," but as "gout," "osteo-arthritis" and "rheumatic gout" were terms used by the older writers in no very clear way, he set himself to inquire whether or not subcutaneous nodules occurred in heterodox as in orthodox rheumatic disorders. "For if they do so occur, one of two conclusions is inevitable. Either rheumatoid arthritis is rheumatism, or the development of fibrous tumours in the subcutaneous tissue is not a special and distinctive note in rheumatism." He formed an opinion to the effect that these nodules "did occur in a distinct proportion of cases of rheumatoid arthritis non-sequential to acute or subacute articular rheumatism"; that they could not be distinguished from the nodules of orthodox rheumatic infection, but that their mere presence did not prove a rheumatic condition. In 1926 Coates and Coombs [11] examined sections cut from nodules removed from cases of infective arthritis, and considered them histologically identical with those of orthodox rheumatic infection. Coates [13] further noted the presence in infective arthritis of the same millet-seed granules he had previously described in rheumatic children. As a further step sections are here described of a bursa removed from a case of infective arthritis, and Professor Geoffrey Hadfield, to whom we are indebted for the production of every section shown, has written as follows:

"This bursa shows subacute productive inflammation which is perivascular in distribution and in one or two places there are localized inflammatory nodules, rich in young capillaries and large endothelial or histiocytic cells. These nodules immediately recall those of an acute rheumatism and do not differ from them essentially in structure."

It now remains to discuss the pathology of other subcutaneous nodules which might be mistaken histologically for those of an orthodox or heterodox rheumatic infection.

Syphilis can be dismissed in a word and is only noted because syphilis was suspected or present in some instances of subcutaneous nodules formerly reported. We now know that syphilis evokes its own typical response.

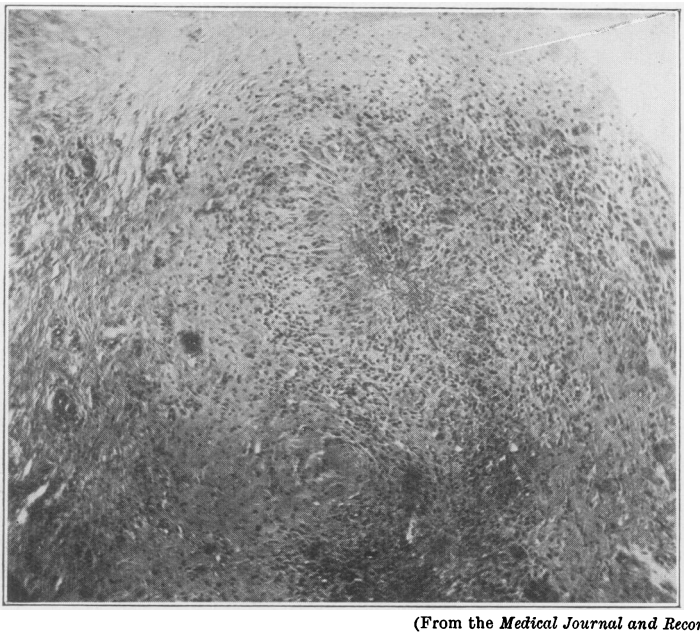
In scleroderma the reaction is essentially fibrous as opposed to the cellular response of rheumatic lesions. The lesions of erythema nodosum bear no resemblance to those of rheumatic infection. The subcutaneous nodules of endocarditis lenta on the other hand, are similar to those under discussion, as has been shown by Coates [11] and Coombs. There is good reason to suppose, however, that endocarditis lenta is a streptococcal disease and, as such, it would in the prevailing opinion fall into line with rheumatic carditis, though its exact relation to orthodox infection is at present doubtful. In respect of subcutaneous nodules in gout, while many of the abarticular subcutaneous lesions are full of bi-urate crystals and are frank tophaceous deposits, yet that type of gout which is apt to masquerade as infective arthritis not uncommonly has subcutaneous nodules true to the rheumatic type. It is not unlikely that this form is what the older writers really meant by "rheumatic gout." The relationship of true gout to orthodox rheumatic infection is not easy to assess correctly, but rheumatic fever occurs in a certain percentage of cases of true gout and clinically gout is not infrequently complicated by infective arthritis or is of such a nature as to defy detection without uric acid estimates or the occurrence of a typical attack. The so-called "nodules," often palpable in the gluteal region of fat women suffering from fibrositis, which give the sensation of



(From the *Medical Journal and Record*)

FIG. 6.—INFECTIVE ARTHRITIS.

Subcutaneous node from a case of polyarthritis with enlarged spleen and glands and achlorhydria. A central mass of necrotic tissue which has become hyaline, surrounded by a fibrocellular zone.



(From the *Medical Journal and Record*)

FIG. 7.—INFECTIVE ARTHRITIS.

Subcutaneous node from a child with fusiform joints, and enlarged glands and spleen. There is central necrosis with peripheral fibroblastic reaction as in the subacute phase of frank rheumatic fever.

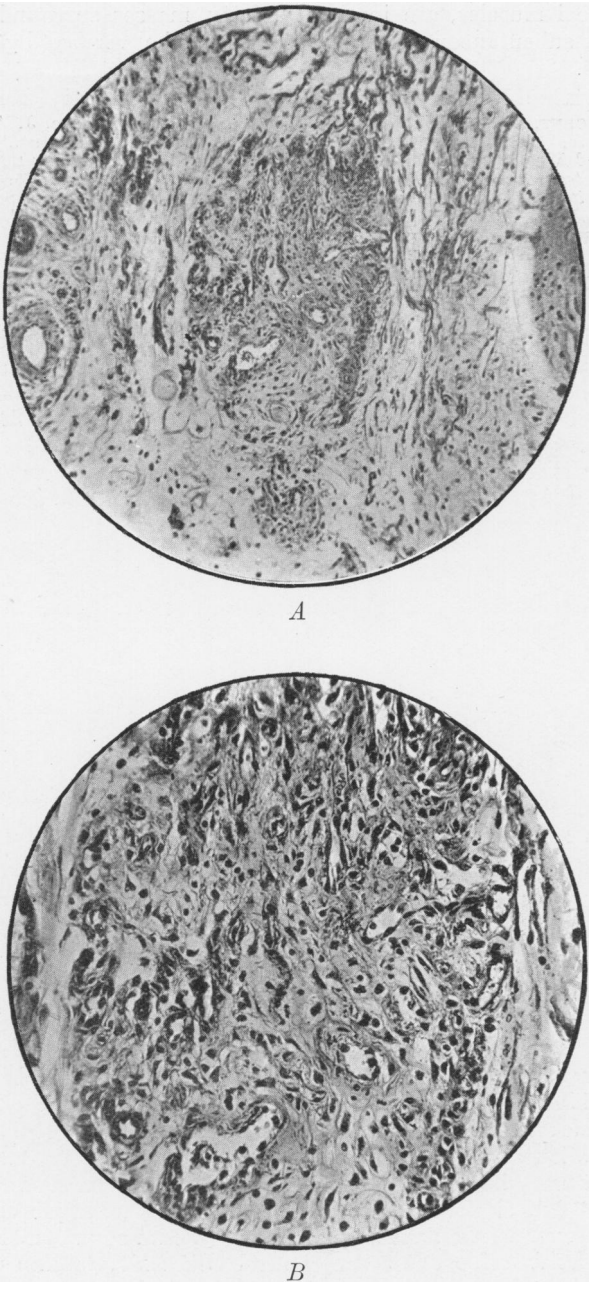


FIG. 8.—INFECTIVE ARTHRITIS.

A.—Low power. *B*.—High power.

Bursa from a woman aged 63 suffering from moderately severe arthritis of scattered distribution. Note the inflammatory nodule rich in young capillaries and endothelial cells essentially the same in structure as those of acute rheumatic fever.

lying in the gluteal muscles, are in reality, fatty masses surrounded by a fibrous envelope in the subcutaneous tissues. This can be verified by transfixion and surgical exposure.

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