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IN REBUS MEDICIS NEMO SAGACIOR.

IN REBUS HUMANIS NEMO HUMANIOR.

OBSERVATIONS ON THE RHEUMATIC NODULE.

BY

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Davaine⁽¹¹⁾ states that subcutaneous nodules were described by Sauvages in the second half of the eighteenth century, but that he did not associate these with rheumatism. It is said by Jaccoud⁽¹⁸⁾ that Froriep was actually the first observer to do this in 1843. Hillier⁽¹⁵⁾ in 1868, wrote copious notes on a boy aged 5, the son of a surgeon, who during the course of an attack of chorea, in which a systolic bruit conducted to the axilla developed, had numerous swellings about the head and joints. His final note is as follows: "This case is a remarkable one from the occurrence of the swellings on the head and near the knee and wrist. They must be regarded as due to rheumatic periostitis." Hillier's case appears to be the first of its type published in England.

Jaccoud⁽¹⁸⁾ in 1871, described rheumatic nodules, their situation and character, and stated that it might be necessary to locate them by palpation. He regarded them as an exceptional feature of rheumatic fever. In 1875, Meynet⁽¹⁹⁾ described the case of a boy with nodules whom he first saw the previous year, and stated that they might be rheumatic or rheumatoid in nature, publishing this case as a curious one of articular rheumatism. In Gerhard's book of children's diseases (1878) Rehn⁽²⁴⁾ describes tumours of the type previously referred to by Meynet, occurring in a girl of 10 with articular rheumatism. In 1881, Hirschsprung⁽¹⁶⁾ described nodes in two children with cardiac disease. In one of these cases nodes from the region of the olecranon consisted of connective tissue with smooth, spindle-shaped and, here and there, larger nuclear cells; and also included copious and in part dilated vessels. There were multinucleated cells and areas with indications of necrobiosis. In 1881 also, Troisier and Brocq⁽²⁵⁾ recorded a case of rheumatic nodules which appeared in separate crops in an adult of 45. In this same year Barlow and Warner⁽²⁾ gave their classical account of subcutaneous nodules, when they described 27 cases, the first being observed in 1875, with histological findings; and among other important conclusions considered "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." In 1883, Angel Money⁽²¹⁾ described an autopsy with subpericardial nodules which were "true homologues of subcutaneous nodules and ought to be called subpericardial nodules." Cavafy⁽⁴⁾, examining a nodule, noted the marked proliferation of the endothelial cells of the vessels therein. Sir Dyce Duckworth⁽¹²⁾ in 1883, was of opinion that several varieties of nodules existed. Mitchell⁽²⁰⁾, working in Osler's Clinic in 1888, was the first to describe a case of subcutaneous nodules in America. Cheadle⁽⁵⁾, writing in 1889, considered that nodules were overlooked for three reasons; (a) they are rarely seen in adults from whom we take our conception of rheumatism; (b) they are not known of or looked for by physicians; and (c) they escape notice by their smallness.

So far, then, the node was generally understood in this country, and was beginning to be realised in America, as a fairly frequent and highly characteristic manifestation of the rheumatic infection of childhood. Further, several writers had dwelt on the essential similarity of these subcutaneous nodes to the inflamed areas of the serous membranes in active rheumatic carditis; an analogy carried further by the careful histological researches of Poynton and Still⁽²³⁾, and further again by a paper⁽⁹⁾ in which one of us (C. F. C.) was able to show that the histological elements of which the subcutaneous node was composed were identical with those of the submiliary nodule (discovered by Geipel⁽¹⁴⁾ in 1905 and by Aschoff in 1906⁽¹⁾) in the rheumatic myocardium; and with the histological units of the changes seen in the rheumatic joint as well as in the serous membranes of the rheumatic heart. The constancy of the reaction of human tissues to rheumatic invasion was thus established, and the subcutaneous node shown to be merely the gross and palpable manifestation of a pathological process repeated in identical form, though on a smaller scale, in other parts of the body. The fact of its similarity to the submiliary myocardial nodule, now generally recognised as developing out of inflammatory changes in blood vessels, has also thrown a good deal of light on the origin of the subcutaneous node. Thus in histological notes on sections of a node made by one of us (C. F. C.), in 1912, the central core of fibrin that has been described by all observers of the structure of the node, is discussed: is it a true inflammatory exudate? or does it arise from coagulation within capillaries? or from rupture and extravasation of a larger vessel? The conclusion of the note is that 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. (Figs. 1, 2, 3, 4, 5.) These characters, the thrombotic centre and the endothelial periphery, stamp the node as a vascular lesion.

To these conceptions of the nature and significance of the rheumatic node little was added for some years, save that American physicians have added their testimony to the characteristic nature and prognostic significance

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 7.

Fig. 6.

of these lesions. In 1895, Fletcher⁽¹³⁾ from the Johns Hopkins Hospital, published a paper, with a good bibliography, dealing with subcutaneous nodes. Bronson and Carr⁽³⁾ divided their series of cases into three groups—(a) Twelve children leaving hospital with apparently complete recovery after rheumatic fever, or at any rate without functional disability, only one of whom showed nodules; (b) nine with a definite carditis, but with the prospect of a fairly normal active life, three of whom had nodules; (c) seventeen with a crippling carditis and chronic cardiac failure, 13 of whom had nodules—of these 17, seven died, six of whom had nodules. The fourth paper from America of any importance is that by Wallace⁽²⁶⁾ in 1924, who stresses the not infrequent occurrence of nodules in Chicago. It must also be remarked that Poynton and Paine⁽²²⁾ were able to grow diplostreptococci from a rheumatic node, and that this has been repeated by Costa⁽⁴⁰⁾ and Irish⁽⁴⁷⁾.

All observations, then, bring us to this point: if there is any one lesion that is characteristic of rheumatic infection, and of severe infection at that, it is the rheumatic node. To this view we have to add some facts that tend to broaden the picture and at the same time to blur its outlines a little.

First, there is the fact already recorded by one of us (V. C.) that many children who present the picture of a smouldering rheumatic infection, yet without clinically demonstrable cardiac lesions, have small subcutaneous nodules which, when removed and examined under the microscope, show the same characteristic tissue reaction. The fact that submiliary nodules occur in the myocardium in rheumatic carditis gave birth to the idea that there might be similar dissemination in other tissues, and the reproduction of the cardiac vegetations in the subcutaneous tissue as nodes pointed towards the likelihood of the same site being affected on a smaller scale by "pocket editions," comparable to the submiliary nodules. A very large number of children was therefore examined over a long period to make practice as perfect as might be, and when it was established that departures from the normal in respect of shotty thickenings and millet seed granules ("Granules" is the word suggested by Dr. Leonard Lees of Clifton) did occur, the investigation⁽⁶⁾ of 100 consecutive out-patient children was undertaken. In 18 out of 23 who gave the usual history suggestive of rheumatic infection nodules were found, but none in the remaining 77 children. Some of these nodules were removed and sections were cut. (Figs. 7, 8, 9.) Subsequently a further investigation⁽⁷⁾ was carried out by one of us (V. C.) in conjunction with Dr. R. E. Thomas and the fact established that these nodules are of very frequent occurrence in children, and the opinion was expressed that they were of diagnostic importance. It was later affirmed, moreover⁽⁹⁾, that these nodules were in point of fact homologous with the submiliary cardiac nodules, and it is now suggested that these demonstrate the existence of a sub-palpable phase of infection. The outstanding feature of these nodules

Fig. 6 is a drawing of subcutaneous nodes by Miss D. Pillers from a patient under the care of (V. C.)

is not their rarity (once there has been sufficient practice in palpating them) but their extraordinary prevalence. Areas exposed to friction or lying over bony prominences are sites at which they can be most easily palpated, the ulnar borders and the vertebral spines in particular. In the former position a to-and-fro, in the latter a lighter rotatory movement of the examining finger has been found to be the best method of feeling nodules.

In what position then do we find ourselves if nodules are as frequent as growing pains? And what is their diagnostic value? The answer is found in a summary of our conception of the rheumatic complex as it occurs in childhood. It is the old parable of the seed and the soil. The seed is ever present in the alimentary tract; the soil is suitable either in virtue of heredity, or because of a lowering of immunity by many factors as yet improperly understood—for example, stress, damp, secondary infection and lack of sunlight. Subcutaneous nodules of the millet-seed order indicate that the barriers of immunity are being successfully assailed and that the result hangs in the balance: either the defence mechanism will recover from its partial dislocation or some added factor, such as a chill, will put it altogether out of gear.

No organisms other than streptococci of low-grade virulence are known to produce a like tissue response to that already described. It is this fact that confers on the subcutaneous nodule its diagnostic importance.

Second, we have severally examined nodes from patients whose other evidences of rheumatic infection were of a heterodox type. The following are selected from these:—

CASE I (under the care of C. F. C.) was that of a youth of 22. At the age of 14, when he came under observation for the first time, he was pale and ill, and had his first attack of polyarthritis with a crop of typical nodes, but no evidence of carditis. This appeared shortly after and ran a severe course, leaving him a crippled heart. In spite of this he got into the Army in 1914 and managed to serve till 1917. Seen in 1920, he appeared to be suffering from endocarditis lenta, with hæmaturia, slight but persistent fever, œdema of the legs, and a few petechiæ. After various attempts to check the course of this had failed, he developed several crops of subcutaneous nodes, one of which over the right elbow (Fig. 10) was removed and sectioned. Soon after this he left hospital at his own request, and made an astonishing recovery, albeit with severe lesions of the aortic and mitral valves. He is still alive and at work. The sections of the node (Figs. 11, 12) showed that it had a kind of racemose arrangement. Its centre consisted of a fusion of several nodal masses and its periphery of two or three others which were separate from each other. Each of these masses had a fibrinous core surrounded by a zone of rich cell production, passing to an outer zone of new vessels and fibrous tissue. The new cells were fibroblasts, with an extraordinarily prolific endothelial reaction producing plasma cells, multinuclear cells, and new blood vessels in every stage of development. In one spot a giant cell of the type seen in tuberculosis was observed. In the fibrinous core of one of the peripheral masses, and less obviously in several parts of the central mass also, the matrix appeared to consist not only of fibrin but also of necrotic debris, in which there were many polymorphonuclear cells. The Gram stain failed to demonstrate cocci.

CASE II. In this instance the node was removed from a patient with a rheumatoid type of arthritis, by Dr. Reginald Miller, who kindly handed it to us for examination. Here, again, the same structures were noted; a central fibrinous core, an intermediate

Fig. 8.

Fig. 9.

Fig. 10.

Fig. 11.

Fig. 12.

Fig. 13.

Fig. 14.

Fig. 15.

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zone of exuberant formation of fibroblasts and endothelial cells, and an outer zone of newly-formed fibrous tissue and capillary blood vessels. (Fig. 13.)

CASE III. This node was removed from a woman of 32 with a cardiac lesion of rheumatic type, a temporary enlargement of the spleen, polyarthritis with a tendency to chronicity in one knuckle, and subcutaneous nodes persisting after all fever and other acute symptoms had died down. For this specimen we are indebted to Dr. Ivor Davies of Cardiff.

Once more, the structure of this node (Fig. 14) is in all respects similar to that of rheumatism in childhood, and exhibits the same tendency to radiate in scattered masses, beyond the limits of the node itself, into the surrounding intermuscular planes of connective tissue.

CASE IV was that of a girl of 13, under the care of one of us (V. C.). She gave no history of rheumatic fever or chorea, but had had pain and swelling in the knees and ankles nine months before. The swelling in the wrists, fingers, and ankles had persisted, and was rheumatoid in type. There was some enlargement of glands and the spleen was palpable. The heart was enlarged but without obvious valvular disease, there was persistent slight fever, bronchitis without tubercle bacilli in the sputum, and some root fibrosis. There was a gross secondary anaemia without leucocytosis. The subcutaneous nodes were very marked. One removed from the elbow, and sectioned, shows a fibrinous centre embraced within a ring of fibroblasts and endothelial cells in all stages of evolution. (Fig. 15.)

The similarity of these nodes drawn from varying sources is attested by the micro-photographs that accompany this article. We are greatly indebted for these to Dr. Geoffrey Hadfield, Pathologist to the Bristol General Hospital, who has given us invaluable help in this as well as in other departments of the present study.

Another point that serves to emphasise our thesis, namely, that the subcutaneous node is not quite so simple and plain an index of rheumatic infection as it seems at first sight to be, is the fact that nodes may occur more frequently in some years than in others. Thus, we have during the past three or four months seen in Bristol as many examples of the rheumatic node as we have seen in the preceding five years. This cannot be ascribed to more careful scrutiny; the nodes have been of such a size and prominence that they could not possibly have escaped notice. Neither is it wholly explained by an increased severity in the type of rheumatic infection. This appears to be partly responsible, but certainly not wholly so. Moreover, these particular nodes have disappeared very slowly, outlasting by weeks all other evidences of active infection.

One final observation we include because it serves to emphasise the fact that a rheumatic infection, as we understand it, is the outcome of many factors. We are not merely dealing with the impact of streptococci on a certain tissue and the reaction consequent on that impact. The form of this reaction, and, in all probability, the impact itself, are both of them the resultant of a number of forces. The observation to which we allude is that of a nodular area over the shin, taken from a patient with chronic ulcerative endocarditis; a lesion which was clinically a compromise between erythema nodosum and an Osler node. Sections of this area showed a central spot of acute polymorphonuclear leucocytosis with necrosis of the leucocytes,

amounting to pus formation; and some fibrinous deposit. Around this was a zone of fibroblastic and endothelial proliferation, infiltrated with many leucocytes. Organisms could not be demonstrated in these sections but streptococci were grown from another similar node.

In this case streptococci, probably of a kind akin to those associated with rheumatic infection, had been thrown into a subcutaneous blood vessel; yet the result was something different from a subcutaneous node. Possibly the node from our Case (I) represents a compromise between the typical node and the lesion just described. At all events it serves to prove that the way in which the organisms enter the tissues which they attack makes all the difference to the lesion that follows; a fact that has to be borne in mind when we are pondering on the difference between clinical rheumatic infection in man and experimental infection of animals with the same streptococci. So far as the clinical manifestations of rheumatic infection are concerned, what we are struck with is not their variability but—on the contrary—their uniformity. It is a wonderful thing that, time after time, the coincidence of certain essentials in the patient's inheritance and environment should enable a streptococcus, which has in all probability only just emerged from a saprophytic existence into a kind of "parvenu" pathogenicity, to inflict on the subcutaneous tissues an injury so constant in type and degree as it is proved to be by the reaction which it excites. We are much impressed by the close similarity to this reaction, of that seen in the nodes which we have described.

SUMMARY.

(1) An account of the steps by which our knowledge of the subcutaneous node of rheumatic infection has advanced to its present position is offered.

(2) The occurrence of tiny granules in the subcutaneous tissues of the rheumatic child is described, and their significance discussed.

(3) Subcutaneous nodes from patients with rheumatoid arthritis, Still's disease, and endocarditis lenta, are described. They are shown to have been histologically identical with those of orthodox rheumatic infection.

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DESCRIPTION OF PLATES.

- Figures 1, 2, and 3. Photomicrographs of a rheumatic node in its early stages, showing exuberant production of new fibrous and vascular tissue.
- Figures 4 and 5. Photomicrographs illustrating later stages in the same process.
- Figure 6. Drawing of subcutaneous nodes from a child with acute cardiac rheumatism.
- Figures 7, 8, and 9. Photomicrographs from sections of the small subcutaneous granules described in the text.
- Figure 10. Photograph of a subcutaneous node on the elbow in a case of endocarditis lenta.
- Figures 11 and 12. Photomicrographs from sections of the same showing its essential similarity to the rheumatic node.
- Figure 13. Photomicrograph of a subcutaneous node from a patient with rheumatoid arthritis; to show its fibroblastic nature.
- Figure 14. Photomicrograph of a subcutaneous node from a case of atypical rheumatic infection, showing changes similar to those in Figs. 1-3.
- Figure 15. Photomicrograph of a subcutaneous node from a case resembling Still's disease. The reaction is similar to that shown in Figs. 1-5.