THE NODULES AND LYMPH-GLAND ENLARGEMENT IN RHEUMATOID ARTHRITIS

ALSO A SYNDROME OF RHEUMATOID ARTHRITIS COMBINED WITH MULTIPLE XANTHOMATOUS CONNECTIVE TISSUE INFILTRATIONS

BY

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In this paper I shall consider the nodules of rheumatoid arthritis and some of the clinical features of cases in which they occur, including the occasional moderate painless enlargement of superficial lymph glands.

Collins (1937) and others have shown that the characteristic subcutaneous nodules consist of foci of fibrinoid degeneration and necrosis, surrounded by a border of tissue reaction, notably by a palisade-like radiate arrangement of fibroblasts. Obviously such a microscopic appearance cannot be absolutely pathognomonic—showing as it does a primitive type of reaction towards a central degenerative or necrotic core of unknown causation, the whole process perhaps commencing as an acute focal exudative lesion. Indeed, similar appearances have been described in granuloma annulare,* and Dr. W. Freudenthal has shown me microscopic sections in illustration, though granuloma annulare is clearly a condition of totally different nature. No exact aetiological explanation of the nodules will be possible before the main causative agent of the rheumatoid disease has been discovered.

The identity of rheumatic fever with rheumatoid arthritis cannot be proved by any histological resemblance between such primitive types of reactive lesions as Aschoff bodies and the relatively transitory “rheumatic nodules” in children suffering from rheumatic fever and chorea on the one hand, and on the other the nodules of rheumatoid arthritis. It is now universally acknowledged that various pathogenic agents (living or not-living) may produce the same reactive or degenerative macroscopic or microscopic picture; also that a resulting lesion may largely depend on, and morphologically vary according to, the reactive qualities of the “soil” on which an identical agent works. It must be admitted on the clinical side that there are subacute or chronic cases of rheumatic fever in adults, especially those affecting mainly the small joints of the hands, which—for a time at least—very much recall the clinical features of rheumatoid arthritis and in which the differential diagnosis may be at first difficult. For

the matter of that it is not always so very easy clinically to differentiate osteo-arthritis (“degenerative arthritis”) from rheumatoid arthritis. Certainly pathological changes of both categories may occur in the same patient, as would seem *a priori* probable. Indeed, one would think that a patient with chronic rheumatoid arthritis is more likely than others to develop some of the degenerative changes of osteo-arthritis, and vice versa. I do not know, however, of any case in which a patient with osteo-arthritis, unmixed with rheumatoid arthritis, has developed subcutaneous nodules (of the rheumatoid arthritis type) or moderate painless enlargement of superficial lymphatic glands (of the rheumatoid arthritis type—see further on). It is said, indeed, that the very rare *large* type of “bone-cyst” above the acetabulum has been found in osteo-arthritis as well as in rheumatoid arthritis. Thus, Burt (1942) illustrates an example in rheumatoid arthritis, whilst Alexis Thomson (1929) figured similar “cysts” as from a case of osteo-arthritis. Of great importance is the fact that patients with symptoms (for a time at least) more or less clinically like those of rheumatoid arthritis may present nodules and juxta-articular infiltrations which on microscopic examination are found not to conform to the rheumatoid arthritis type. But to this subject I will return further on.

Some Case Histories

I have mainly selected rather “exaggerated” examples, in which in addition to ordinary changes of chronic rheumatoid arthritis there were subcutaneous nodules—in one case a smaller nodule, more cutaneous than subcutaneous, could be examined by biopsy—enlarged synovial bursae with thickened walls, ganglia of the hands or wrists, juxta-articular thickenings of tendon insertions or tendon-sheaths, and moderate painless enlargement of superficial lymphatic glands.

CASE 1

Mrs. A. B. Aged 56 years. Has had rheumatoid arthritis for 25 years. The chief changes are in the hands and wrists. Large wrist ganglia. Lesser changes in the feet, elbows, and knees. Subcutaneous nodules about

* I understand that microscopically the so-called “lipoid necrobiosis” (not confined to diabetics) is a somewhat analogous necrotic lesion, but containing lipoids.

affected joints. Large lobulated ones at the elbows are connected with the olecranon bursae. Small ones over knuckles of fingers and toes and over both patellae. These latter, which developed rapidly and almost painlessly within the last weeks, feel like tense cysts and are not definitely attached either to the cutis or to the periosteum. There is a large, fluctuating, ganglion-like swelling at the back of the right wrist from which there are hernia-like protrusions. Blood count: Hb. 58 per cent.; erythrocytes 3,900,000 per c.mm.; C.I. = 0.73; leucocytes 10,400 per c.mm. (polymorphonuclears 58 per cent.; lymphocytes 31 per cent.; monocytes 5 per cent.; eosinophils 5 per cent.; basophils 1 per cent.). Blood-Wassermann reaction: negative. Urine: nothing special. Brachial blood pressure: 150/90 mm. Hg. Blood cholesterol: 220 mg. per 100 c.cm. Blood urea: 30.5 mg. per 100 c.cm. Blood uric acid: 4.1 mg. per 100 c.cm. Basal metabolic rate: ± 10 . There is moderate painless enlargement of lymphatic glands in both axillae. No enlargement of liver or spleen. Some pyorrhoea alveolaris. Nothing else of importance by ordinary examination. Recent dietetic treatment for gastric ulcer has been successful.

A

early necrosis is taking place: here and there are many degenerated neutrophil leucocytes as well as a smaller number of coarsely granular eosinophils. Lymphocyte and plasma-cell infiltration is present in the lymphatics of the dermis. No giant-cells seen." The photomicrographs (Fig. 1, A and B) show a necrotic centre with radiate reactive border of the "rheumatoid arthritis type."

CASE 2

C. D. Aged 48½ years. An office clerk (Weber, 1943; Case 2). Rheumatoid arthritis of three years' duration. Large cutaneous-subcutaneous nodules about the joints, with juxta-articular infiltrations in the tendon sheaths and fibrous structures about the feet, ankles, hands, wrists, elbows, and knees. Most striking are the red shiny nodules over the metacarpo-phalangeal articulations and about the elbows—up to the size of large cherries (Fig. 2). The knees, ankles, and feet are similarly affected, but the nodules are less red. Very characteristic are the nodules along the ridge of the ulna of both forearms, from elbow to wrist. Moderate painless enlargement of the inguinal, axillary, and supracondylar lymphatic glands. No obvious splenomegaly. None of the nodules are really painful or tender. The tendon sheaths at various parts are infiltrated, notably in the palms and at the heels

B

FIG. 1. Case 1: Photomicrograph from a section of the left olecranon bursa, which has been transformed into a lobulated massive nodule of the "rheumatoid arthritis type." It shows a necrotic centre with radiate reactive border. A. Under low power. B. Under high power.

Biopsy.—My colleague, Mr. H. Rast, kindly excised the whole of the subcutaneous, enlarged, lobulated left olecranon bursal mass, in which there was only a minute synovial cavity left. The bursa was transformed into a mass of small hard nodules, one of which was so superficial as actually to be in the cutis. The mass was elongated, measuring 6.5 cm. (in length), 3.5 cm. (in width), and 2 cm. (in depth), and on incision presented an anaemic, whitish, somewhat gelatinous appearance. Following is Dr. J. G. Greenfield's histological report (see Fig. 1 A and B): "The central core of the tissue consists of a structureless unnuclated—i.e., necrotic—tissue which in Van Gieson sections shows a varying amount of collagen. In some places it forms a loose network, in others thicker strands. The outlines of old obliterated blood vessels can also be recognized. Round this core there is a dense wall of viable collagen (i.e. nucleated connective tissue with thick collagen fibres), with a palisaded zone of radially arranged fibroblasts between the viable and necrotic tissue. In one place

(Achilles tendons). The distribution of the nodules and infiltrations is markedly symmetrical. There is some stiffness at the back of the neck, and owing to the condition of the knees the patient cannot bend forward properly. The hands are stiff and show some subluxation of joints. The fingers are said to turn dark blue nearly every morning in cold weather. Ordinary examination of the thorax, abdomen, and urine shows nothing special. Erythrocyte sedimentation rate greatly accelerated. Blood-Wassermann and Kahn reactions negative. The blood cholesterol is rather on the low side. The teeth were all removed at least twelve years ago. About that time the patient was found to have a duodenal ulcer (confirmed by x-ray examination).

Biopsy.—microscopic examination of one of the nodules (Fig. 3) shows connective-tissue reaction, with foci of fibrinoid degeneration and necrosis, surrounded by palisade-like, radiate borders of fibroblasts, as described by Collins (1937) in regard to the subcutaneous nodules of rheumatoid arthritis.

FIG. 2. Case 2 : Photograph of nodules on upper limbs, July, 1941.

CASE 3

E. F. Aged 59 years. English. A stonemason, working at present as a post-office packer. Rheumatoid arthritis of at least five years duration. On the whole, however, an active man, of "wiry" type. Hard subcutaneous nodules about the size of an olive over ulnar ridge near either elbow, of about six months' duration, not painful, but slightly tender to pressure. Moderate, painless, symmetrical enlargement (the patient was unaware of this) of lymphatic glands in axillae and groins. No enlargement of spleen or liver. Tense, cyst-like,

pea-sized, painless nodule over the proximal interphalangeal joint of the right fourth finger, which appeared about twelve months ago, suddenly (as patients say such small nodules of rheumatoid arthritis do). This was a cutaneous rather than a subcutaneous nodule. He also has moderate flabby enlargement of the right olecranon bursa, which hurts slightly if he leans on it. Some stiffness and ulnar deviation of the fingers of the right hand. Slight stiffness in cervical spine. He had other symptoms formerly that disappeared under treatment. No history of gonorrhoea or syphilis. Nothing special by ordinary examination of thorax, abdomen, nervous system, and urine. Slight anaemia. Blood sedimentation: slightly accelerated. Blood-Wassermann reaction: negative. Blood cholesterol: 345 mg. per 100 c.cm. Blood calcium: 9 mg. per 100 c.cm. Blood urea: 43 mg. per 100 c.cm. Blood uric acid: 3.2 mg. per 100 c.cm.

Biopsy.—My colleague, Mr. H. Rast, excised the above-mentioned nodule from the knuckle of the right ring-finger, and it was carefully examined by Dr. W. Freudenthal. It showed multiple foci of so-called "fibrinoid degeneration" and necrosis (as described by Collins, 1937), some of them surrounded by a palisaded border of fibroblastic reaction; elastic fibres practically absent from the degenerative areas; no giant-cells seen.

Remarks

Even if the histological features of the nodules of rheumatoid arthritis were absolutely pathognomonic one would still be far from the discovery of the essential pathogenic agent of the disease. But, as I have already pointed out, the type of lesion in question cannot be regarded as really pathognomonic. Allison and Ghormley (1931) (compare also Ghormley, 1938) made a great point of what they call "focal collections" of lymphocytes in the synovial membrane of joints being almost pathognomonic of "proliferative arthritis of uncertain origin"—that is to say, of rheumatoid arthritis. They write (p. 139): "Diagnosis made positive on discovery in the tissues of focal collections of lymphocytes." But if one looks at their illustra-

FIG. 3. Case 2 : Photomicrograph of a section from a subcutaneous nodule showing typical necrotic focus with radiate fibroblastic border.

tions (for instance, p. 147, Fig. 4; p. 169, Fig. 3; and Plate VIII) one recognizes the presence in these "focal collections" of so-called "germ-centres" of Flemming. Now, surely such lymphadenoid foci with typical "germ centres" can hardly be considered as pathognomonic of any special disease. Apart from their conspicuous presence in normal lymphadenoid tissue (lymph glands, tonsils, the walls of the vermiform appendix and intestines, the Malpighian corpuscles of the spleen), they form a special feature in so-called lymphadenoid goitres, and are also not rare in thyroids from patients with Graves's disease. I have seen them in abnormal salivary glands. They constitute a conspicuous feature of cutaneous lymphocytomata (Epstein, 1935), and may be found in various other pathological conditions.

The Painless Lymphadenopathy

Neither is there anything absolutely pathognomonic in the painless lymphadenopathy of the superficial lymph glands, which is present in many cases of rheumatoid arthritis, though seldom noticed by the patients themselves and often not looked for by the examining doctor. I myself have had a biopsy in only one of my cases, but I believe that the finding is typical for other cases also—namely, a non-specific "follicular lymphadenopathy" of toxic or infective origin, with marked enlargement of the "germ-centres" of Flemming. This must of course not be confused with the early stages of "follicular reticulosis" or "follicular lymphoblastoma" of non-inflammatory (neoplastic) origin.

CASE 4

Mrs. G. H. Aged 65 years. Of thin, wiry build, was under treatment in 1941 and 1942 for rheumatoid arthritis. She had suffered from lobar pneumonia of the right upper lobe in the spring of 1939. In Sept., 1940, she began to suffer from rheumatoid arthritis, afterwards located notably in the hands, with some fusiform swelling of the finger-joints. There was also considerable stiffness of the cervical spine. Some moderate discrete painless enlargement of superficial lymph glands in neck, axillae, and groins, of which patient herself was unaware. No enlargement of spleen or liver. Brachial blood-pressure: 190/90 mm. Hg. Some hypertrophy of the left ventricle of the heart, apparently from high blood-pressure. Trace of albumin in the urine. Blood count (July 1, 1941): Hb. 65 per cent.; erythrocytes 3,580,000 per c.mm.; C.I.=0.91; leucocytes 6,150 per c.mm. (polymorphonuclears 71 per cent.; lymphocytes 21 per cent.; monocytes 6 per cent.; eosinophils 1 per cent.; basophils 1 per cent.).

Biopsy.—On Sept. 12, 1941, Mr. Rast excised one of the enlarged lymph glands from the right axilla. Dr. J. G. Greenfield's microscopical report (Fig. 4) is: "The sections show general proliferative activity, with many mitoses, in the lymphoid centres; and occasional collections of polymorphonuclear cells in relation to the sinusoidal systems. There is also a slight fibrosis of the gland. These are all evidences of toxic or bacterial stimulation of no specific type."

When the patient left the hospital on Nov. 13, 1942, she could walk almost normally, and no enlargement of

FIG. 4. Case 4 : Photomicrograph of a section from an enlarged lymph gland showing toxic or infective "follicular lymphadenopathy" with large germ-centres.

any superficial lymph glands could be felt, excepting the inguinal glands, and that very slight and on the right side only.

A Syndrome of Rheumatoid Arthritis Combined with Multiple Xanthomatous Connective-Tissue Infiltrations

There are other subcutaneous nodules and infiltrations which might in rare cases be confused with those of rheumatoid arthritis (Weber, 1943), but I shall here confine myself to a condition which seems to be genuine rheumatoid arthritis associated with multiple xanthomatous nodules and infiltrations, especially about the joints and in the subcutaneous (occasionally cutaneous) tissue.

The special case that I shall fully record here has been under observation for several years. I described it originally with Dr. W. Freudenthal in 1937 and later in 1943 (Weber and Freudenthal, 1937; Weber, 1943), but can find no literature on the subject excepting perhaps Layani's case of "Xanthomatous chronic deforming rheumatism" (Layani, 1939; Layani and others, 1939). Layani's case was that of a woman, aged 46 years, who had a deforming rheumatoid disease of fifteen years' duration. In addition to the xanthomatous condition she had prolonged jaundice with hepatomegaly, and there were other remarkable features in the account.

However, owing to the kindness of Dr. George Graham and Dr. E. T. D. Fletcher, I have been able to examine two other men in England apparently suffering from a somewhat similar syndrome. I

hope that an account of these two cases will appear in due course. As I have been given kind permission to refer to these cases with my own one, I will here emphasize the point that hypercholesterolaemia seems not to be an essential, and is certainly not a constant symptom. Another point is that the infiltrations tend to be greatly in excess of those generally recognized as an occasional feature in typical rheumatoid arthritis. In all three cases there was strong evidence that the application of heat made the xanthomatous infiltration worse. This was pointed out to me by Dr. Graham from various observations in his own case, and it may be of some therapeutic significance. Dr. Fletcher's patient believes that radiant-heat therapy (which was given previously to seeing Dr. Fletcher) had made his trouble rather worse than better. Both my patient and Dr. Graham's patient developed a florid increase of the subcutaneous infiltrations—which tended to become actually confluent in parts over their shoulders and backs (the specially hot parts) after they had been lying for days on their backs in bed. Another remarkable feature in both Dr. Graham's patient and mine was the occurrence (in addition to the large and medium-sized nodules) of minute (miliary) superficial nodules ("droplets"), evidently arising in the outer part of the cutis; these appeared for a time in great numbers on the nose, forehead, and other parts of the face, and then disappeared without leaving a trace. In my case the ultimate atrophy or involution of the large nodular infiltrations tended to be more complete than that which occurs in acknowledged cases of rheumatoid arthritis. Finally, I cannot help thinking that the xanthomatous infiltrations in these little-known cases may have a relation to the rheumatoid arthritis analogous to that which gouty tophaceous deposits sometimes appear to have to osteo-arthritis with

exaggerated Heberden's nodes. It may be remembered, by the way, that Chauffard and others (1921 and 1923) found that tophaceous deposits contained a considerable admixture of cholesterol. In Dr. Graham's case a large sarcoma-like growth ultimately developed. This reminds me of the possible though doubtless exceedingly rare relation of sarcoma to benignant so-called "xantho-myeloma of tendon sheaths," and perhaps it might also be compared to the very rare supervention of frank spindle-celled sarcoma in "multiple idiopathic haemorrhagic sarcoma" of Kaposi (which is generally considered not to be a true sarcoma). I well remember this occurring in an old case of Sequeira's (Sequeira and Brain, 1926).

CASE 5

This case was demonstrated by Parkes Weber and Freudenthal at the Royal Society of Medicine in Dec., 1936 (Weber and Freudenthal, 1937), under the heading "Nodular non-diabetic cutaneous xanthomatosis with hypercholesterolaemia," but the presence of cholesterol in the lesions was not absolutely proved, and the hypercholesterolaemia was certainly not constant. Following is the account of the case up to the time of the demonstration in 1936.

K. L. A man aged 35, general labourer, began six months ago to suffer from pains and stiffness in various joints, which obliged him to give up work. Since then he has had varying swelling of the knee-joints and of the tendon sheaths at the back of the wrists, now hardly noticeable. During the last six months cutaneous nodules (freely movable over the deeper parts) have been appearing on the hands, mostly on the back of the fingers and thumbs, especially near the joints; they are hard and reddish, averaging a small pea in size (Fig. 5). During the same period similar nodules appeared over the ulnar ridges, up to the size of a cherry over the right olecranon (Fig. 6); two pieces were excised for biopsy purposes from the left elbow, and one pea-sized nodule from over

FIG. 5 Case 5 : Photograph of the right hand, Nov. 14, 1936.

FIG. 6. Case 5 : Photograph of the right elbow, Nov. 14, 1936.

the base of the left index finger. Numerous smaller nodules are to be seen over the external ears, and still smaller ones (really miliary or minute) on the face, especially over the borders of the lips and nostrils. Some of the minute facial nodules have a yellowish-red colour. None of the nodules have been itching or painful or tender to pressure, except the large ones at the elbow. Recently, in December, fresh nodules, mostly red, have appeared about the elbows, over the back of both great trochanters, over the buttocks, and over the coccyx in the intergluteal fold. There is now also a conglomerate or confluent nodular plaque over the back of both acromial regions—more pronounced on the right side, on which the patient usually lies. It is highly probable, as I stated above, that this florid exacerbation of the subcutaneous infiltrations was induced by local heat due to the patient lying for days in bed. His body-weight is 53.2 kilogrammes, against (apparently) 60 kilogrammes early in November.

There is nothing especial in the past history, excepting dysentery in 1920 in India. The patient was kindly handed over by Dr. M. B. Ray, and he was in hospital under my observation from Nov. 14, 1936 to April 1937.

In the hospital there was occasional slight fever in November. By ordinary examination of the thorax and abdomen and by x-ray examination of the thorax and bones of the hands and feet, nothing abnormal is found; nor is there anything special to be noted in regard to the nervous system and eyes (fundi normal) and internal parts of the ears, nose, and mouth (including pharynx). There is no thickening of the ulnar nerves at the elbows. The urine shows nothing abnormal (unless very slight excess of urobilinogen), and no alimentary glycosuria follows the ingestion of 50 g. glucose. Fasting blood sugar: 0.07 per 100 c.cm. Blood-sugar curve normal. Blood-serum cholesterol on the first occasion was 230 mg. per 100 c.cm., and on the second 350 mg. per 100 c.cm. Fractional examination of the gastric contents shows complete absence of free hydrochloric acid even after a subcutaneous injection of histamine; pepsin

present. The blood serum, which is clear but somewhat over-coloured, gives a negative direct, but positive indirect, Van den Bergh reaction. Wassermann and Meinicke reactions: negative in the blood. Pirquet cuti-reaction: negative. Blood sedimentation: not decidedly accelerated. Blood urea: 36.5 mg. per 100 c.cm. Blood uric acid: 3.7 mg. per 100 c.cm. Non-protein nitrogen in the blood: 30.5 mg. per 100 c.cm. Blood-serum calcium: 8.5 mg. per 100 c.cm. Blood count (Nov. 24): Hb. 84 per cent; erythrocytes 4,500,000; leucocytes 3,500 per c.mm. (eosinophils 7 per cent.; polymorphonuclear neutrophils 45 per cent.; lymphocytes 45 per cent.; monocytes 3 per cent.).

Biopsy.—Histological report by Dr. W. Freudenthal (Figs. 7, 8): The main change seen in the sections is the presence of large masses of cells, which form round, or oval more or less, defined areas, and are scattered irregularly between the bundles of the collagen tissue in all parts of the cutis. The cells are so numerous that their mass exceeds that of the collagen tissue, the bundles of which are pressed aside rather than destroyed. These cells are conspicuous by their size, which is up to four times that of an epithelial cell. Most of them are multinucleated and have three to five or more bright nuclei (with definite nucleoli), frequently aggregated. They have a well-stained, well-defined, abundant, round, oval or polygonal cytoplasm. Most of the cells are clearly defined; sometimes neighbouring cells are connected by cytoplasmic threads giving them a certain resemblance to prickle cells. The cytoplasm is homogeneous; even by oil-immersion magnification it does not show a foamy structure.

When the sections are stained for fat with Sudan III, these cells in some areas show no fat or lipoid at all; in other areas the cytoplasm is stained a faint red, which is in some places more distinct. No double refraction. Even in the areas in which the cells are stained more distinctly the colour is paler than the bright red of the fat cells of the subcutaneous tissue; the colour of the supposed xanthoma cells has the slightest tinge of brown.

FIG. 7. Case 5 : Photomicrograph of a section from an excised nodule. The epidermis is seen in the upper part of the figure, and the large size of the "pre-xanthoma cells" is obvious by comparison with the size of the epidermis cells.

In fact, it is a question whether the cells ought to be called xanthoma cells at all, for by the term "xanthoma cell" one usually understands a cell the cytoplasm of which is loaded with lipoid droplets ("foam cells"). In our sections the cells show either no lipoid (visible by our imperfect histo-chemical method) or lipoid in a

diffuse form. Merely to call these cells giant-cells would scarcely help us. One could perhaps call them "pre-xanthoma cells" to mark their connexion with typical xanthoma cells. It must be admitted that we have no proof that these cells actually become xanthoma cells. A possible explanation is, then, that these cells represent an intermediate stage in the development towards typical foam cells (cf. Arzt, 1919). Yet it is possible that they are not an intermediate stage, but are at the height of their development, and that their peculiar appearance is due to some special lipoid they contain. Microscopically, it must be admitted, they show a marked resemblance to "Gaucher cells."

Progress of the Case after Dec., 1936.—Under a fat-poor diet the blood-serum cholesterol fell to 110 mg. per 100 c.cm. (Feb. 19, 1937), and the nodules decreased, notably the patches over the back of the acromial regions. The patient finally left the hospital in April, 1937. When he was seen again in April, 1941, at the age of 40½ years, there were only remnants of the nodules on the hands and about the elbows. The process of involution had left a little shrivelling of the skin about the left elbow. Rheumatoid troubles were in the foreground, but even in regard to these he thought he was improving. He could get about, but owing to stiffness in the hips he could not stoop sufficiently to pick up anything on the floor. His fingers were rather stiff and slightly deformed. There was some limitation of movement in the left shoulder and a little crackling on movement could be felt over the joint and left scapula. Both knee-joints manifested considerable crackling on movement. The appetite was good. The patient said he was treated at the Middlesex Hospital about 1938–39, where he had all his teeth removed, a fat-poor diet, orange juice with glucose, massage, and injections of some kind.

On Nov. 6, 1943, I was able again to examine the patient, K. L., who said that he was able to walk about well and do night watching (without any medical treatment). In short he had functionally almost recovered, although he could not yet flex his right hip normally. He still had "knotty" rheumatoid hands, with nodules at the knuckles and over the elbows. There was also a good deal of crackling when he flexed and extended his knee-joints.

FIG. 8. Case 5 : Photomicrograph of a section from an excised nodule. Hair follicle on the left.

CASE 6

In June, 1941, a married sister of the patient was seen, Mrs. M. N., aged 43, who was said to be suffering from a chronic rheumatoid disease. She is a well-built woman of about 10 st. 4 lb. in weight. There is chronic thickening of both wrists with limitation of movement. Both elbow-joints cannot be properly extended. The right knee is somewhat flexed and there is crackling on movement. The left knee seems normal. There is thickening around the proximal interphalangeal joint of the left little finger and apparently some infiltration of its flexor-tendon sheath. No other joints are affected, and there are, and have been, no cutaneous or subcutaneous nodules. She has had twelve children, of whom ten are living and well. Her rheumatoid troubles commenced in both hands eighteen months after the birth of her third child, that is to say, about sixteen and a half years ago. She has never had pain in connexion with them she says, except a little aching in rainy weather, and she has never really been laid up. It is possible that her condition is similar to that of her brother, but a very incomplete form of the disease.

Summary

In this paper the nodules, infiltrations, and painless adenopathy of rheumatoid arthritis, and their pathological significance, are considered.

Attention is also drawn to the existence of a little-known syndrome in which clinical features of rheumatoid arthritis are associated with nodules and infiltrations, apparently of xanthomatous nature, though hypercholesterolaemia seems to be of not necessary (at least, not constant) occurrence. I have described only one case fully (which was first

observed many years ago), but I know of the existence of other cases probably of the same category, two of which will, I hope, be fully described in due course. The interest of this syndrome does not lie in its extreme rarity, but rather in the light which, when more completely studied, it is likely to throw on the pathology and nature of various other groups of cases.

My thanks are due to Dr. George Graham, Dr. M. B. Ray, and Dr. Ernest T. D. Fletcher for enabling me to see and helping me to examine some of the patients, to Mr. H. Rast for carrying out the biopsy excisions, to Dr. W. Freudenthal and Dr. J. G. Greenfield for their microscopic reports and to Dr. Greenfield for photomicrographs, and to the Editors of the *British Journal of Dermatology* and the *Proceedings of the Royal Society of Medicine* for allowing me to use previous papers of mine and blocks for illustration.

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