THE SUBCUTANEOUS NODULES AND THE VISCERAL LESIONS OF CHRONIC RHEUMATOID ARTHRITIS.

A Thesis

Presented in part fulfilment
of the Requirements for the Degree of
Doctor of Medicine
of the University of Cape Town

by

Marshall Horwitz.

B.Sc., M.B., Ch.B. (Cape Town).

Department of
Clinical Medicine,

University of
Cape Town.

1948.

I N D E X.

SECTION III. - THE SUBCUTANEOUS NODULES OF RHEUMATOID ARTHRITIS.

SECTION 1.

INTRODUCTION.

A. INTRODUCTION.

During recent years increasing attention has been paid by many workers to the various visceral lesions which may be encountered in cases of chronic rheumatoid (atrophic) arthritis. The clinical features of rheumatoid arthritis, including generalized wasting, pyrexia, tachycardia, painful muscles, paraesthesiae and vasomotor disturbances had always suggested that a disturbance was present which was not limited solely to the joints. HENCH has often expressed the view that rheumatoid arthritis was a generalized disease with special joint manifestations. The biopsy, biochemical and autopsy findings described by various observers have tended to confirm this important suggestion. The problem of rheumatoid arthritis has become somewhat analogous to that of generalized sclerodema which affects not only the integument but also many, if not most, of the organs of the body. (GOETZ, 1945).

Lesions have been described in the heart, in skeletal muscles and in peripheral nerves in cases of chronic rheumatoid arthritis. Clinicians have noted various changes in the skin and in the eyes. The presence of splenomegaly or of lymphadenopathy or of both has been known for many years. The

characteristic subcutaneous nodules have been described with their pathological and clinical features by various observers. Several investigators have noticed the occurrence of amyloidosis as a complication of the disease. Laboratory investigations have produced evidence of impairment of hepatic function. Gastro-intestinal abnormalities have been described. Renal lesions have been noted at autopsy in some series of cases. All these features indicate that rheumatoid arthritis is a widespread disease with variable degrees of systemic involvement.

Although a fair amount of work has been done in regard to these problems there still appears to be place for fresh contributions to the subject. Many of the observations reported have not yet been widely confirmed nor generally accepted, and additional data would be of value in helping to reach more complete conceptions. Several examples can be given to indicate the value of further investigations. There is a paucity of reports on the clinical, electrocardiographic and radiological features of the heart in cases of chronic rheumatoid arthritis, and the subject has become of great interest and importance in view of the fairly high incidence of rheumatic heart disease reported at autopsy. The subcutaneous nodules have been fairly extensively studied but WEBER (1944)

is of ...../

is of the opinion that "further biopsy examinations will furnish us with data of clinical, and specially diagnostic, value". Interesting lesions have been described by a few workers in the skeletal muscles and, at this investigation is still very recent and is still in the experimental stage, further contributions might reveal information of additional value. The study of these 3 problems constitutes the major part of this thesis.

An important defect in much of the published work on the visceral lesions has been the concentration by the various workers on one particular visceral lesion in the cases examined. Pathologists, for example, have reported on the autopsy findings in the heart but have not attempted close correlation with other visceral lesions. It would be interesting to know, for example, whether cardiac lesions occur in significantly greater numbers in cases of rheumatoid arthritis with subcutaneous nodules than in cases without them.

If an investigator interested in a particular field, e.g. in haematology, collects and selects all cases of rheumatoid arthritis with splenomegaly and with leucopenia, he may compile a group of cases which might be, and which have been, designated by various names. The error which may be made, and which

is not ...../

is not clearly appreciated, is that the investigator has been specially on the lookout for such cases and that his conclusions are therefore not a true reflection of their incidence or of their importance. In this way various names have come into general use such as "Felty's Syndrome" which may not necessarily be warranted. If observers reviewed the overall incidence of various visceral lesions instead of collecting and recording cases with particular associated features then their results would reflect the position more accurately. There is thus valuable information to be gained from a general clinical, laboratory and radiological investigation of a series of cases by one observer to help in determining the incidence of the various visceral lesions. Such a contribution would be a guide to what a clinician engaged in investigating or in treating rheumatoid arthritis might expect to encounter in a series of unselected cases. The results, too, would be of use in avoiding the erroneous designation of new, or the perpetuation of old, syndromes.

While the study of the subcutaneous nodules and the visceral lesions is the prime object of the thesis, the clinical features of the cases studied were carefully noted in order that they could be compared with the generally accepted descriptions.

Here, .../

Here, too, there is room for fresh contributions, e.g. there is a wide difference of opinion on the incidence of involvement of the terminal interphalangeal joints in the disease. It would be of interests, too, to determine whether the clinical features of the disease as seen in the climatic conditions of Cape Town differ in any way from the cases reported in Great Britain and the United States. FINN (1948) claimed that "rheumatoid or atrophic arthritis is an almost non-existent disease" in South Africa, but this thesis should serve to eradicate any erroneous impressions which this statement may have caused locally or overseas. The investigation also offers an opportunity to contrast the findings of the disease in the European and Non-European populations of Cape Town and to determine whether there is any difference in the pattern of the disease in the Non-European.

B. THE PROBLEMS TO BE INVESTIGATED.

The subject of this thesis is thus the detailed study by means of clinical, laboratory, radiological and special investigations of the subcutaneous nodules and of the visceral lesions encountered in chronic rheumatoid arthritis. Autopsy examinations would, of course, reveal data of more precise and accurate value, but patients with the disease usually live for many years and opportunities for postmortem examinations are rare.

The study of the cases will include a complete examination, and points of interest which emerge from the investigation will be discussed. Particular attention will be paid to the presence or absence of skin and nail changes, ocular lesions, lymphadenopathy and splenomegaly. The sedimentation rate of all the cases, including those which are still "active" clinically and those which are apparently "burnt-out" will be investigated. The relationship of "Felty's Syndrome", "Still's Disease", "Psoriatic Arthritis" and "Arthritis Mutilans" to "classical" chronic rheumatoid arthritis will be reviewed in relation to the findings noted in the series of cases.

The subcutaneous nodules will be the subject of especially careful attention and the following features will be noted: incidence, distribution, physical characteristics, duration, relation to state of

"activity" ...../

"activity" of the arthritis, relation to trauma and histological appearances, etc. Investigations will be performed to determine the presence of absence of calcification, lipoid deposition and amyloid deposition in the nodules. The findings will be illustrated by photographs to indicate the main features demonstrated. The nodules will be briefly compared with the subcutaneous nodules encountered in other diseases.

There are a few interesting cases of nodules with lipoid deposition described in the literature: the reports will be carefully analyzed to determine whether or not these particular nodules have a common etiology and pathogenesis, and new data will be added as a result of further investigations.

Examination of the cardiovascular system to determine the incidence of rheumatic heart disease will include the following procedures: full clinical examination of the heart in different postures, using the ordinary bell and the Bowles stethoscopes, electrocardiography, radiological examination of the heart and phonocardiography.

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The muscle lesions will be investigated by deltoid muscle biopsy. A series of control cases will be examined to aid in the assessment of the value of the procedure in the diagnosis of rheumatoid arthritis.

Biochemical investigations will be performed to determine the presence or absence of amyloidosis and to detect any abnormality of hepatic, renal or gastric secretory function.

Finally, the various lesions will be tabulated and the results analysed to determine whether there are any special inter-relationships between them.

C. MATERIAL.

A total of 70 cases of chronic rheumatoid arthritis (synonyms, chronic atrophic arthritis, arthritis deformans) were examined and investigated. The vast majority, viz. 64 cases, were examined during the 18 months between March, 1947 and August, 1948 while the thesis was being prepared. A smaller number, viz. 6 cases, were seen between 1943 and 1946 and were less completely investigated. All these cases were examined personally. The cases in the major group (64 cases) were all examined on at least 2 occasions, the usual interval between the examinations being approximately one year.

Source of Origin of the Cases.

The sources of origin afford some general indication of the severity, the duration and the degree of crippling and disability of the cases.

(a) 22 cases were seen as in-patients in Groote Schuur Hospital;

(b) 20 cases were seen at the Conradie Home, Pinelands (a home for the chronic sick).

(c) 19 cases were seen as out-patients at the Arthritic Clinic, Groote Schuur Hospital.

(d) 8 cases were seen at the Medical

Out-patients...../

Out-patients Department, Groote Schuur Hospital.

(c) 1 case was seen as an in-patient at the New Somerset Hospital.

All the cases of definite chronic rheumatoid arthritis which were seen personally during the periods stated above were included in the series and no case was omitted when the results were compiled. There was no special selection of certain types of cases and the series has not been "loaded" with cases of a particular type: e.g. a case of chronic rheumatoid arthritis with psoriasis was encountered in the series, but the dermatology wards and clinics were not specially combed for similar cases as they would then assume an undue magnitude in the series.

Selection of Cases.

Very careful attention was paid to the clinical features to exclude other types of polyarthritis and to ensure that the cases were examples of true idiopathic chronic rheumatoid arthritis. It is not possible to be absolutely certain of the diagnosis of chronic rheumatoid arthritis as there is no single pathognomonic clinical feature or diagnostic laboratory test. This is a difficulty encountered by all writers and investigators in this subject. However, the clinical pattern is

sufficiently...../

sufficiently characteristic on the whole to permit of ready identification. The criteria laid down by the Committee of the American Rheumatism Association (Primer on Arthritis, 1942) have been carefully followed in the selection of the cases. The 70 cases in this series all fulfilled these criteria. They were cases of symmetrical polyarthritis, very often with involvement of the fingers and wrists and knees, usually insidious in onset, with a prolonged progressive course, tending to involve new joints, and leading, after a variable period, to varying degrees of deformity and contractures.

All the cases had polyarthritis, i.e. multiple joints were affected. It is well-known that classical chronic rheumatoid arthritis may commence as a monoarthritis and the true nature of the disease may only become obvious by its subsequent progression. However, while the disease is still limited to one joint, or to 2 joints, there is always the difficulty of differentiation from other types of arthritis (e.g. gonococcal arthritis, tuberculous arthritis, etc.) Therefore no cases of monoarthritis have been included.

All the cases were of at least 6 months duration. Very early cases have not been included as it is in this group, too, that the differential diagnosis from other arthritides may be difficult. Several other investigators of the visceral lesions in chronic

rheumatoid ...../

rheumatoid arthritis have also excluded these early cases from their series.

The clinical diagnosis was supported by confirmatory radiological evidence in 66 cases. In 56 of these 66 cases there was unquestionable evidence of some or all of the characteristic radiological abnormalities, viz. osteoporosis, narrowing of joint space, areas of cortical erosion, subluxations, fibrous or bony ankylosis, etc. In 10 cases the only radiological finding was fusiform periarticular soft tissue swelling, compatible with the diagnosis of rheumatoid arthritis. In 4 cases no radiological examinations of the affected joints was performed but the clinical diagnoses were unquestionable.

Exclusion of Cases.

(a) Osteoarthritis: There was no difficulty in excluding cases of osteoarthritis from the series as the clinical and radiological features were quite distinct. A few cases were seen during the past 18 months in which the diagnosis between rheumatoid arthritis and osteoarthritis was uncertain: these cases are not included in the series of 70 cases. In 2 cases there were secondary osteoarthritic changes radiologically, but the clinical picture, evolution of the disease, and the other radiological features were so indubitably characteristic of rheumatoid arthritis that these cases were included in the series. These

cases ...../

cases illustrate the well-known fact that the radiological features of osteoarthritis (hypertrophic arthritis) may become superadded on to primary arthritic disorders such as gout, haemophiliac haemarthroses, rheumatoid arthritis, etc.

(b) Brucellosis: The Editors of the "Ninth Rheumatism Review" (1948) state that in their experience "brucellosis is about the last thing to think of as the cause of chronic arthritis of the rheumatoid type". "Arthralgia is common in brucellosis and temporary non-purulent joint inflammation may occur, but brucellosis is seldom, if ever, the cause of chronic non-purulent joint inflammation" was the conclusion reached by GREEN and FREYBERG (1941). Nevertheless, it was decided to perform the brucella agglutination reaction in most of the cases. The test was performed in 47 cases and was negative in all.

(c) Ankylosing Spondylitis: While the 70 cases of classical chronic rheumatoid arthritis were being investigated, 7 cases of ankylosing spondylitis were encountered. The diagnosis was obvious on clinical examination and was confirmed radiologically

in ...../

in each instance by the demonstration of sacro-iliitis and calcification of the ligaments around the apophyseal joints and around the vertebrae. Some of these cases had involvement of the peripheral joints which appeared identical with the changes found in chronic rheumatoid arthritis. However until the exact relationship between rheumatoid arthritis and ankylosing spondylitis becomes clearly defined, it was decided not to include cases with ankylosing spondylitis in the series.

(d) Gout: 11 cases of gout were diagnosed while the rheumatoid arthritis series was under investigation. The diagnosis was irrefutably proved in 9 of these cases by the demonstration of sodium biurate crystals in tophi. In the remaining 2 cases the diagnosis was practically certain on clinical, radiological and biochemical grounds, but there were no tophi to be examined. These 11 cases of gout presented certain features which will be discussed when the subcutaneous nodules and visceral lesions of rheumatoid arthritis are reviewed.

In compiling the series of 70 cases of chronic rheumatoid arthritis it was essential to avoid the inclusion of cases of gout. In none of the cases did the history, the course or the physical findings suggest the diagnosis of gout. Both gout and rheumatoid arthrit may have areas of erosion of bone radiologically, often

referred ...../

referred to as "punched out areas", but the general pattern and other important radiological features usually permitted a radiological distinction between the two diseases. The serum uric acid was estimated in 50 cases of the series of rheumatoid arthritis. The results varied between 1.3 mg. per cent and 5.9 mg. per cent, the average level being 3.4 mg. per cent. In only 5 cases of chronic rheumatoid arthritis did the serum uric acid exceed 5 mg. per cent and in no case did it exceed 6 mg. per cent. Although normal serum uric acid levels can occur in gout, yet the combination of (i) the clinical picture of classical rheumatoid arthritis; (ii) radiological features of the disease and (iii) normal serum uric acid, served to make it practically certain that no cases of gout were included in this series.

(e) Syphilis: Although syphilitic arthritis and synovitis are comparatively rare entities, the Wasserman reaction was performed on 59 cases in the series. It was negative in each instance with the exception of a known case of tabes dorsalis (Case 25).

(f) Specific Infective Arthritides: No cases of purulent, pyaemic or tuberculous arthritis were included in the series.

There was a past history of gonorrhoea in Case 36, 34 years before the onset of the rheumatoid arthritis...../

arthritis. The Editors of the Ninth American Rheumatism Review (1948) discuss the problem of cases of so-called "gonorrhoeal arthritis resistant to penicillin." They expressed the opinion that many of these cases were examples of rheumatoid arthritis in men who also happened to have gonorrhoea or of rheumatoid arthritis precipitated, reactivated or aggravated by genital gonorrhoea. This was shown by the frequent development of new articular sites and by the slow development of symmetrical fusiform polyarthritis of the rheumatoid arthritis type. Similarly, if a polyarthritis develops many years after an attack of gonorrhoea and fails to respond, it is usually regarded as an example of rheumatoid arthritis, not of gonococcal arthritis.

There was no history or evidence of pneumonia, bacillary dysentery, meningococcaemia, typhoid fever, lymphogranuloma inguinale or other causes of specific infective arthritis in the cases included in the series.

During the investigations pulmonary tuberculosis was encountered in 2 instances. This finding will be discussed when the clinical features of the series of rheumatoid arthritis cases are reviewed.

"So-called ...../

"So-called Infective Arthritis": the usual concept of this condition is that it is an arthritis following in close temporal relationship to the development of an obvious focus of infection - sometimes called "focal infection arthritis" or "infective arthritis". "In such cases articular involvement tends to be asymmetrical; large, rather than small joints are predominantly affected; there is little or no tendency to progression; a chill and fever may occur at the onset; the disease is self-limiting and the prognosis is better than in rheumatoid arthritis".

The Editors of the Ninth American Rheumatism Review (1948) are divided in their opinions as to whether this entity is just a variety of acute and subacute rheumatoid arthritis or whether it is a more specific condition. It is partly on account of the nature of this problem that the cases accepted for discussion in this thesis have all had the disease for at least six months.

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Other cases are included in this thesis for special reasons which are indicated in the text. A numbered list of all the cases studied, together with the diagnoses, is included at the end of the thesis in order to facilitate reference.

TABLE 1.

Summary of the Cases Studied.

Rheumatoid Arthritis	70 cases
Ankylosing Spondylitis	7 cases
Gout	11 cases

D. METHODS.

All the cases were subjected to a full clinical examination including urine analysis. Special investigations were performed on the vast majority of the cases, but all the methods of special investigation were not always performed in each case.

The following special investigations were carried out on the 70 cases studied. The numbers in the brackets indicate the number of cases in which each investigation was performed.

1. Electrocardiography (59)
2. Phonocardiography (45)
3. Radiography of the heart (55)
4. Biopsy of Subcutaneous Nodules (19)
5. Muscle Biopsy (34)
6. Blood Count (57)
7. Sedimentation Rate (Westergren's Method) (63)
8. Congo Red Test (15)
9. Liver Function Tests.
   - Thymol Turbidity (49)
   - Colloidal Gold (48)
   - Thymol Flocculation (44)
   - Serum Proteins (46)
10. Blood Urea (21)
11. Serum Cholesterol (20)
12. Serum Uric Acid (50)
13. Fractional Test Meal (23)

1. ELECTROCARDIOGRAPHY. (59).

Electrocardiograms were recorded with a "Sanborn Cardiette" in 39 cases and with a "Sanborn Viscocardiette" in 20 cases.

In each case the three standard limb leads were used. The standard limb leads were as follows:

Lead I - one electrode on the right arm and the other on the left arm (RA to LA).

Lead II - one electrode on the right arm and the other on the left leg (RA to LL).

Lead III - one electrode on the left arm and the other on the left leg (LA to LL). (KATZ, 1946).

In addition to the standard limb leads, leads IVR, CF_2, CF_4 and CF_5 were used in 50 cases. In accordance with the "Joint Recommendations on Standardization of Precordial Leads of the Special Committee of the American Heart Association and the Cardiac Society of Great Britain and Ireland," (KATZ, 1946), the following nomenclature was used:

Lead IVR: one precordial lead was placed upon the extreme outer border of the apex beat, as determined by palpation. (If the apex beat could not be located satisfactorily by palpation the electrode was placed in the fifth intercostal space just outside the left border of cardiac dullness, or just outside the left midclavicular line if percussion of the heart was

unsatisfactory. ..../

unsatisfactory.) The electrode was paired with an electrode placed on the right arm.

Leads CF_2, CF_4 and CF_5: The precordial electrode was paired with an electrode placed on the left leg. The position of the precordial electrode was indicated by the subscript used according to the following plan:

(a) Subscript 2 was used for the left margin of the sternum in the 4th. intercostal space;

(b) Subscript 4 was used for the left midclavicular line at its junction with the 5th. intercostal space;

(c) Subscript 5 was used for the junction of the left anterior axillary line with a horizontal line down from CF_4 around the left side of the chest. (KATZ, 1946).

Electrocardiographic tracings were recorded at least once in each of the 59 cases. In addition the tracings were recorded on a "Sanborn Cardiette" on a second occasion in each of 23 cases after an interval varying between 3 months and one year.

The tracings were taken with the patients recumbent to avoid the possibility of producing prolongation of the PR interval in the erect posture.

The sensitivity of the beam was adjusted until it deflected 1 cm. per 1 millivolt.

2. PHONOCARDIOGRAPHY. (45)

Electrophonocardiograms were recorded with a "Sanborn Phonocardiogram" in 45 cases. The tracings were recorded with the electrodes connected to the right arm and the left leg, i.e. Lead II. The amplifier for the heart sounds was placed on 3 sites in each case, viz.

(a) Over the aortic area in the 2nd. right interspace;

(b) in the 3rd. left interspace just lateral to the left margin of the sternum. This site was selected on account of the frequent propagation of the diastolic murmur in aortic regurgitation down the left border of the sternum;

(c) over the apex.

Tracings were recorded in each case at each site at the usual electrocardiographic speed and at a thrice-magnified speed.

In order to avoid missing diastolic murmurs, the tracings at the aortic area and at the 3rd. left interspace were taken with the patients sitting forwards and also with the patients recumbent. The tracings from the apex were recorded at rest and also after the patients had exercised and had turned slightly on to their left sides. These manoeuvres are commonly used i

clinical...../

clinical medicine to facilitate the detection of the diastolic murmurs at these areas.

.. ..

All the electrocardiographic and phonocardiographic tracings were recorded and developed personally to avoid technical errors in the procedures.

3. RADIOGRAPHY.

PA and oblique views were taken of the hands and wrists in 66 cases in order to confirm the clinical diagnoses and to demonstrate the special radiological features. The plates were taken with the standard nonscreened technique.

Teleradiographic examinations of the heart were made in 55 cases. The deformities of the joints resulted in inability to get some of the patients into the suitable position for the right and left oblique views and for screening. Thus, in 23 of the 55 cases, only PA views of the heart were taken. ROGEN (1947) noted similar technical difficulties in his cases and was unable to continue the radiological investigations.

4. BIOPSY OF SUBCUTANEOUS NODULES. (19).

This was performed under local anaesthesia with 2 per cent procaine. The biopses were performed in an operating theatre under conditions of strict asepsis. The overlying skin was cleaned with ether, rectified spirits, acetone and tincture of iodine. The procaine was injected superficial to the nodules, deep to the nodules and on each side of the nodules, but care was exercised to avoid injecting the solution into the nodules and perhaps disturbing the architecture.

During the dissection the relationship of the nodules to the overlying skin, to bursal lining, to periosteum and to the subcutaneous tissue was noted. After dissection the nodules were examined macroscopically and were measured. A small portion was excised from each nodule, pulverised and examined microscopically for the presence of sodium biurate crystals. This procedure was employed as an additional precaution against the inclusion of cases of gout in the series of rheumatoid arthritis. No urate crystals were found in any of the subcutaneous nodules of the patients with rheumatoid arthritis.

The subcutaneous nodules were then promptly fixed in 10 per cent formaline-in-saline and later embedded in paraffin wax. Sections from each nodule were stained with haematoxylin and eosin.

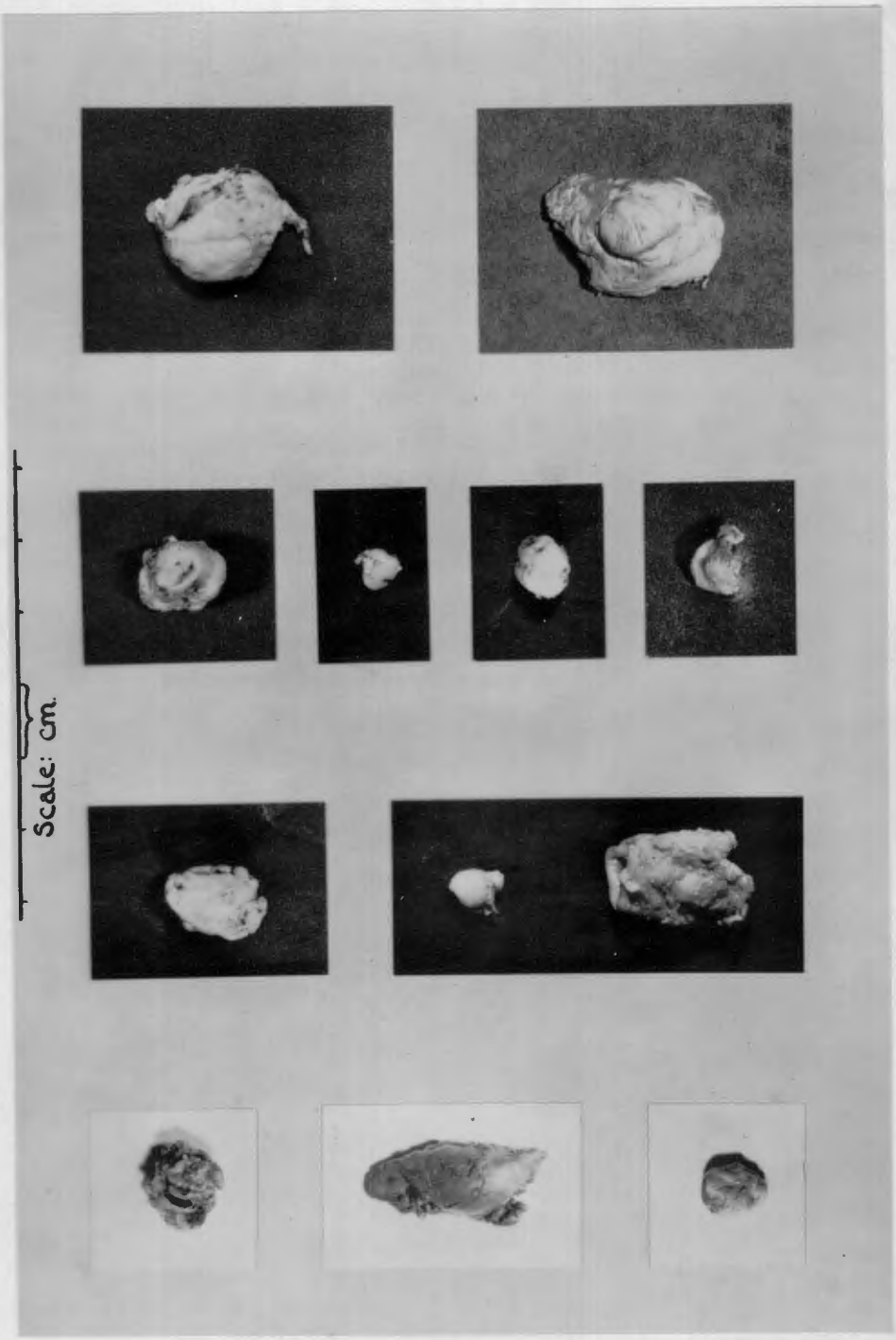
In addition...

Of the 70 cases of rheumatoid arthritis which were examined, 20 cases had one or more nodules. Biopsies were performed in 15 of the cases. In 14 cases one nodule was removed; in one case, 3 nodules were removed and in one case 2 nodules were removed. A total of 19 nodules was thus removed for histological examination. Fig. 1 illustrates the sizes and general appearances of 12 of these 19 nodules.

In addition fresh frozen sections were taken from 10 nodules and stained with Scarlet Red to demonstrate the presence or absence of lipoid.

FIG. I

12 of the 19 Subcutaneous Nodules.



5. MUSCLE BIOPSY. (34).

This was also performed under local anaesthesia with 2 per cent procaine. The deltoid muscle was selected as the biopsy site in 33 cases as it is easily accessible. In one case the biopsy was taken from the gastrocnemius muscle during the manipulation of the knee joints under general anaesthesia.

The muscle biopsies were also performed under conditions of strict surgical asepsis and the overlying skin was cleansed in the usual manner. After an incision approximately 2 inches long was made through the skin and the subcutaneous tissue it was found convenient to insert an Allport's mastoid self-retaining retractor to obtain a good exposure of the deltoid muscle fibres. Two parallel linear incisions were made into the muscle belly, about ½" apart and about one inch in length. A curved aneurysm needle was passed down into one incision and pushed gently up through the second incision. In this way a portion of muscle was elevated and could easily be removed with the aid of a dissecting forceps, scalpel and pair of scissors. The size of an average piece of muscle removed in this manner was approximately ½" long, ¼" broad and ¼" thick. In some cases it was easier to remove 3 smaller pieces which together totalled the same

size...../

size. As far as possible trauma to the portion of the muscle to be examined was carefully avoided.

It was found advisable to have an assistant to aid in the retraction of the subcutaneous tissue and to aid the securing of haemostasis. Haemorrhage from the muscles ceased spontaneously or was easily controlled by catgut sutures. After the skin incision was stitched with silkworm gut a dry sterile gauze dressing was applied. This was covered with cottonwool and a firm elastoplast dressing applied to minimize haematoma formation. All the incisions healed by first intention and the skin stitches were removed on the eighth day after the biopsy.

The biopsy specimens were fixed in corrosive sublimate and embedded in paraffin wax. Sections were stained with haematoxylin and eosin.

6. BLOOD COUNT. (57).

A complete blood count (including white cell count, red cell count, haemoglobin estimation, volume of packed cells and blood smear) was done in 37 cases. In twenty cases the blood count was limited to white cell count, red cell count and blood smear.

The purpose of performing the blood counts was to obtain data to be used in the discussion of the visceral lesions and not to conduct a complete investigation into the features of the anaemia often present in rheumatoid arthritis.

The methods used were the usual ones employed in haematology (WHITBY and BRITTON, 1946).

Oxalated blood was used for the red and white cell counts. For the red cell count a dilution of 1/200 was made. Hayem's fluid was used as the diluting fluid. A 1/50 dilution was used for the white cell count. The cells were counted on both sides of a "Spencer Bright Line" counting chamber.

Red cell counts were expressed in millions per cubic millimetre (cu. mm.). White cell counts were expressed as the number of white cells per cu. mm. Differential white cell counts were recorded as the percentage of each type of white cell present.

The haemoglobin estimations were performed with a Haldane haemoglobinometer in 25 cases and with a Zeiss haemoglobinometer in 12 cases.

The ...../

The volume of packed cells (V.P.C.) was measured by Wintrobe's Method (1946). 5 ml. of blood was inserted into a tube containing a mixture of 4 mg. solid potassium oxalate and 6 mg. solid ammonium oxalate. The V.P.C. was expressed as a percentage.

7. SEDIMENTATION RATE (Westergren's method). (63)

The standard technique was adopted. .4 cc. of 3.8 per cent sodium citrate solution (the anticoagulant) was drawn into a syringe. The needle on the syringe was then introduced into a vein and 1.6 cc. blood withdrawn into the syringe. The mixture was emptied into a specimen tube and gently manipulated to ensure thorough mixing. The blood was then drawn, without further delay, into a standard Westergren tube, graduated in mm. of length. The blood was drawn up to the zero mark which was 200 mm. from the point. The tube was set upright in a stand in which a spring clip, pressing on the top, held the point firmly against a piece of rubber at the lower end. The tube was left to stand in an exactly vertical position. The upper level of the red cell column was read at the end of one hour. The result was reported as the distance sedimented in mm. by the top of the red cell column.

Great care was taken to ensure that there was no contamination of the blood with ether or methylated spirits as SYKES (1948) has shown that their presence interferes with the results of the test. The syringes and needles were boiled and then cleaned with sterile normal saline before use.

Westergren's ...../

Westergren's method was used as it is easy to perform. Its general reliability is well recognised and recently SINTON (1948) produced evidence to show that it was more useful than Wintrobe's method in estimating the degree of activity and the progress of a group of tuberculous cases. FLETCHER (1947) strongly recommended the use of Westergren's method for determining the sedimentation rate in cases of rheumatoid arthritis.

The normal figures are not more than 3 mm. at the end of one hour in the case of males, and not more than 7 mm. at the end of one hour in the case of females (COMROE, 1944). FLETCHER (1947) doubts, from his personal experience, whether there is any justification for giving separate figures for the 2 sexes; he regards the upper limit of normal for both sexes to be 8 mm. at the end of one hour.

The problem arose as to whether the sedimentation rate should be corrected for anaemia. WHITBY and BRITTON (1946) consider that no method of correction is entirely reliable. BUTLER et al (1938) have concluded that anaemia has little effect on the phenomenon of blood sedimentation. FLETCHER (1947) discusses the problem at some length and considers that correction of the sedimentation rate for anaemia is best avoided. In this series no corrections have been made for anaemia.

The following investigations were performed with the assistance of the Department of Clinical Pathology, University of Cape Town:

8. CONGO RED TEST. (15).

5 cc. blood were removed by venupuncture from the patient. Then .1 G. congo red dissolved in 10 cc. saline was injected intravenously. After 4 minutes, 5 cc. blood were removed by venupuncture and a further 5 cc. blood were removed one hour after the commencement of the test. 3 different sets of syringes and 3 different needles were used in each case to avoid accidental contamination with congo red. As far as possible different veins, or different sites in the same vein, were selected for each venupuncture.

The test was performed according to a modification of the method of TARAN and ECKSTEIN (1942).

The results were expressed as the percentage of congo red present at 4 minutes which was detected after one hour.

9. LIVER FUNCTION TESTS.

(a) Colloidal Gold. (40).

(b) Thymol Turbidity. (47).

(c) Thymol Flocculation. (26).

These 3 tests were performed according to the method of McLAGAN (1944). The colloidal gold should normally be 0, and the thymol turbidity should not exceed 3.

(d) Serum Proteins. (46).

Serum albumen and globulin were estimated by a modification of Fine's biuret method (1935).

10. BLOOD UREA. (20).

Urea estimations were performed by CONWAY's urease method (1933).

11. SERUM CHOLESTEROL. (20).

This was estimated according to a modification of the method of MYERS and WARDELL (1918).

The normal serum cholesterol by this method varies between 120 mg. per cent and 250 mg. per cent approximately.

12. SERUM URIC ACID. (50).

Serum uric acid estimations were performed according to a modification of BROWN's method (1945). The upper limit of normal by this method is 6 mg. per cent.

13. ...../

13. FRACTIONAL TEST MEAL. (23).

This was carried out in the standard way. After fasting overnight, a Ryle stomach tube was passed and the gastric contents aspirated. 300 mg. of caffeine citrate in 300 cc. of water were given by mouth and specimens withdrawn from the stomach at 15 minute intervals for 3 hours. The 6th. specimen was tested for acid and if none was present histamine acid phosphate 0.5 mg. was injected subcutaneously.

The free acid was titrated with N/10 NaOH, using Topfer's reagent as indicator. The results were expressed in the usual units, i.e. cc. of n/10 NaOH required to neutralize the acid in 100 cc. of gastric juice.

The results were expressed as follows (HARRISON, 1937):

"Achlorydia - never any free HCL".
"Hypochlorydria - free HCL never above 10 cc. N/10 per cent".
"Hyperchlorydria - one or more points on the curve above 60 cc. N/10 per cent".

SECTION II.

CLINICAL FEATURES OF CHRONIC RHEUMATOID ARTHRITIS.

A. AGE INCIDENCE.

The ages varied widely between 9 and 77 years. Table 2 indicates the distribution of the various age groups.

TABLE 2.

ANALYSIS OF AGE INCIDENCE.

Ages	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
Cases	1	4	4	12	17	15	13	4

This distribution of the age groups approximates the distribution in Rogen's series of 33 cases (1947).

The average age in the series of cases was 47.

B. SEX INCIDENCE.

There were 47 females and 23 males in the series, i.e., there were almost twice as many females as males. This incidence is in conformity with the usual findings in most series of cases of rheumatoid arthritis.

C. RACIAL INCIDENCE.

The series consisted of 44 Europeans and 26 Non-Europeans (23 of whom were Cape Coloured and 3 of whom were Malays).

These findings indicate that the disease occurs in the Non-Europeans with a frequency not very dissimilar to that encountered in the Europeans. It would be inadvisable to attempt to conclude that the disease is less common in Non-Europeans on the basis that they constituted a minority of the total group in this series. A possible explanation for the difference in numbers might be the greater ability or desire of the Europeans with arthritis to receive hospital or institutional treatment.

There were no major differences noted between the sex and age incidence in the European and in the Non-European groups.

D. DURATION.

The duration varied between 7 months and approximately 45 years. The average duration for the entire series was approximately 7 years; for the female cases 8 years; and for the male cases 6 years.

The average duration of the male cases in Rogen's series (1947) was 3 years, which is less than the average duration in this series. The average duration of his female cases was 9 years, which is about the same as in this series.

Table 3 indicates the distribution of the duration of the cases.

TABLE 3.

ANALYSIS OF DURATION OF ARTHRITIS.

Duration in years	½-1	1	2	3	4	5	6	7	8	9	10	11-20	21-30.
Cases.	6	9	7	6	2	8	5	3	7	-	2	11	4

It is ...../

It is apparent that only a minority of the cases, i.e., 15 cases, are more than 10 years in duration, More than half of the cases are less than 6 years in duration. The series thus includes a wide range of cases, some being early and others very advanced.

Of the 15 cases in which the duration was more than 6 years, 6 were seen at the "Conradie Home for the Chronic Sick". The inclusion of all the cases seen at the Conradie Home thus did not greatly modify the distribution of the durations, although, on the whole, they were cases of the more advanced type with grosser degrees of deformity and ankylosis.

E. ONSET.

It is not easy to define the terms "gradual onset" and "acute onset" accurately. Different authors have probably had different opinions of the meaning attached to these terms. In this thesis the term "insidious" or "gradual onset" will be used to indicate that the arthritis developed slowly and insidiously over several weeks or several months, and that it may or may not have been preceded by prodromal symptoms. The term "acute onset" will be used to indicate that the arthritis appeared as rapidly and as suddenly as do cases of rheumatic fever, acute gonococcal arthritis or acute gout, i.e., the arthritis appeared on a particular day or developed rapidly over a few days or weeks. A helpful clinical indication in differentiating between the two types of onset is the ability, or inability, of the patient to continue his work and his activities during the first few weeks and months of the illness. The division can obviously not be clear cut. In this series 8 cases were acute in onset while the vast majority (62 cases) were gradual in onset. This finding corresponds to some extent with Comroe's statement that the onset is acute in less than 10 per cent of cases (1944).

F. PAST HISTORY OF RHEUMATIC FEVER OR PREVIOUS ATTACKS OF ARTHRITIS.

Only one case (Case 24) had a past history of rheumatic fever one year before the onset of the chronic polyarthritis. The attack of rheumatic fever was accompanied by pericarditis and by pleurisy.

An interesting feature was elicited in the history of 3 cases, (Cases 2, 5 and 11). The duration of the disease in these 3 cases were 6, 5 and 10 years respectively. Each had suffered from previous attacks of chronic polyarthritis which had persisted for a few years followed by complete remissions until the relapses developed. Minor and moderate fluctuations are, of course, well-known in the disease, but these 3 cases are examples of the complete temporary remissions which are known to occur.

.. ..

The progress and spread of the disease in each of the cases was typical of rheumatoid arthritis, and the extent and nature of the joint involvement resembled the published accounts closely. The only striking

feature ...../

feature noted in this series was the comparatively high incidence of involvement of the terminal interphalangeal joints, and this will be more fully discussed.

6. INVOLVEMENT OF TERMINAL INTERPHALANGEAL JOINTS.

It is usually stated by most authoritative observers that the terminal interphalangeal joints are very rarely involved in rheumatoid arthritis. COMROE (1944) states that "one rarely sees clinical evidence of damage in distal interphalangeal joints". FLETCHER (1947) discussed the joint involvement in 254 cases of "infective arthritis". (He apparently is using this term to indicate rheumatoid arthritis). He found that "the terminal interphalangeal joints were never affected" in this large series of cases. The Committee of the American Rheumatism Association (Primer on Arthritis, 1942), endorsed these views by stating that "for some reason the terminal interphalangeal joints usually escape."

On the other hand certain pathological studies on the joints at autopsy have indicated that the terminal joints are often involved in the disease. (BENNETT, KELLER and BAUER, 1940). COMROE (1944) discusses the problem and quotes the pathological evidence that the terminal joints are involved by the same inflammatory

process...../

process which affects the proximal interphalangeal joints.

The Editor of the "Ninth Rheumatism Review" (1948), is apparently still unwilling to accept the reported involvement of the terminal joints, as he added the personal comment "uncommonly" after reviewing an article which mentioned that involvement of the terminal joints may occur in rheumatoid arthritis.

It is not very easy to be certain of the presence or absence of involvement of the terminal joints clinically. It is important to realise that the terminal joints normally become almost immobile if the proximal interphalangeal joints are held in the position of full extension on account of pain, swelling or ankylosis. As involvement of the proximal joints is very common it follows that there will often appear to be diminished movement and stiffness of the terminal joints on clinical examination. Subsequently the terminal joints could conceivably develop some degree of periarticular fibrosis from disuse. Therefore, in this investigation I have not diagnosed involvement of the terminal joints if the sole clinical feature was stiffness.

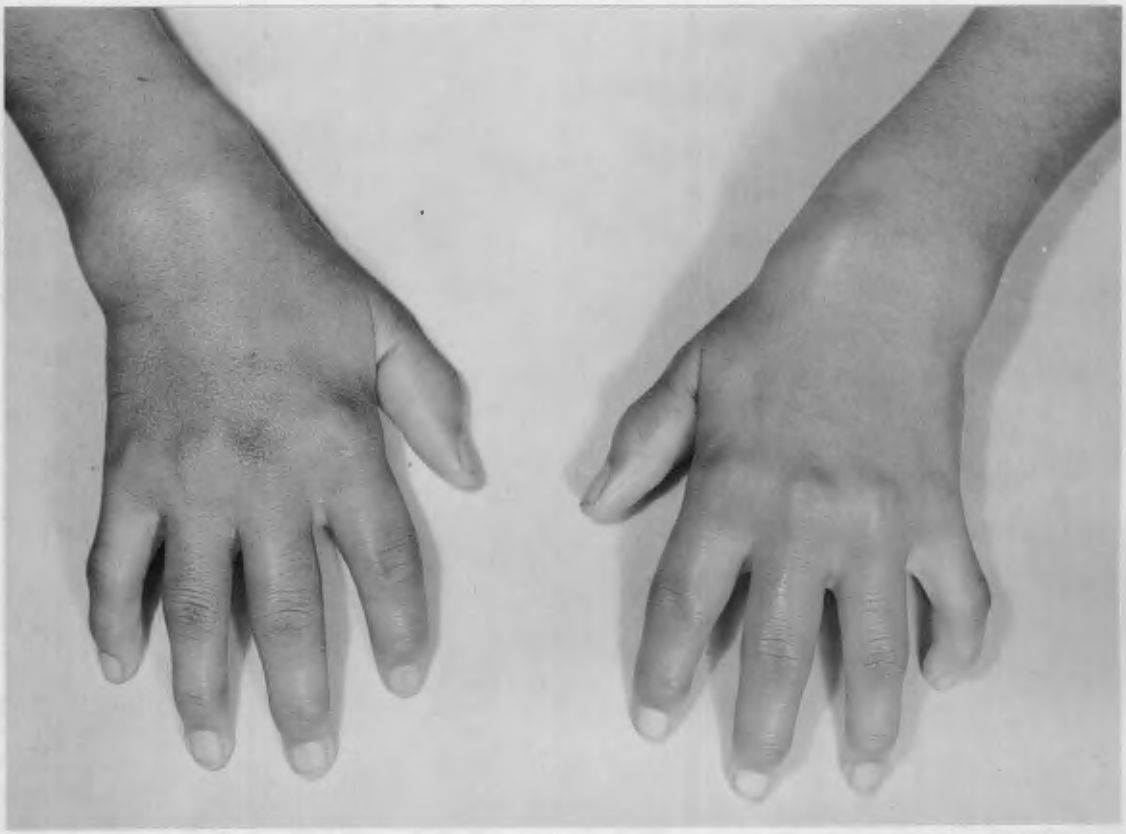
However, in 14 cases the patients stated in their histories that they had experienced pain at some time or another in the terminal joints. In 5 of these 14

cases...../

cases the terminal joints were swollen. Fig. 2 illustrates this involvement of the terminal joints clinically in a girl aged 17. In 6 of the 14 cases there were abnormal radiological changes in the terminal joint, viz. narrowing of joint space, atrophy of the adjacent ends of the phalanges, and, in some cases, bony ankylosis. The appearances were not those which are seen in osteoarthritis affecting the terminal joints.

FIG. 2.

Involvement of Terminal Interphalangeal Joints.



Case 27 : Chronic Rheumatoid Arthritis.

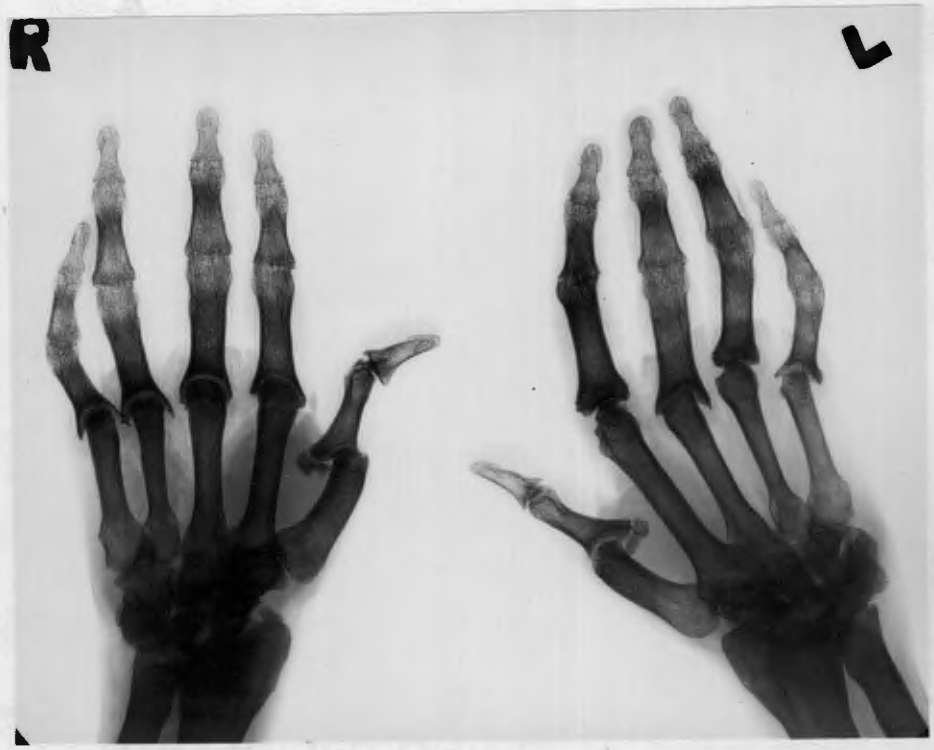
The metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints are all swollen.
"Carpal cysts" are present on the dorsum of both wrists.

Figs. 3, 4, 5, 6, (of Cases 2, 51, 3, and 61 respectively) indicate these abnormal radiological features.

The analysis of the 14 cases with evidence, either clinical or radiological, of involvement of the terminal joints is interesting. One case had psoriasis and will be referred to again. Nine of the cases were seen at the Conradie Home and were thus examples of the more advanced crippling cases of the disease. Three of the remaining cases had suffered from the disease for 16, 17 and 35 years respectively. It therefore appears that involvement of the terminal joints is mainly liable to develop in either the longstanding cases or in the severely incapacitated, deformed cases encountered in institutions for the chronic sick. The incidence of involvement of the terminal joints may perhaps thus develop on the sites where the patients are seen, and this fact may explain the different incidence in this series of cases.

FIG. 3.

Involvement of the Terminal Interphalangeal Joints.

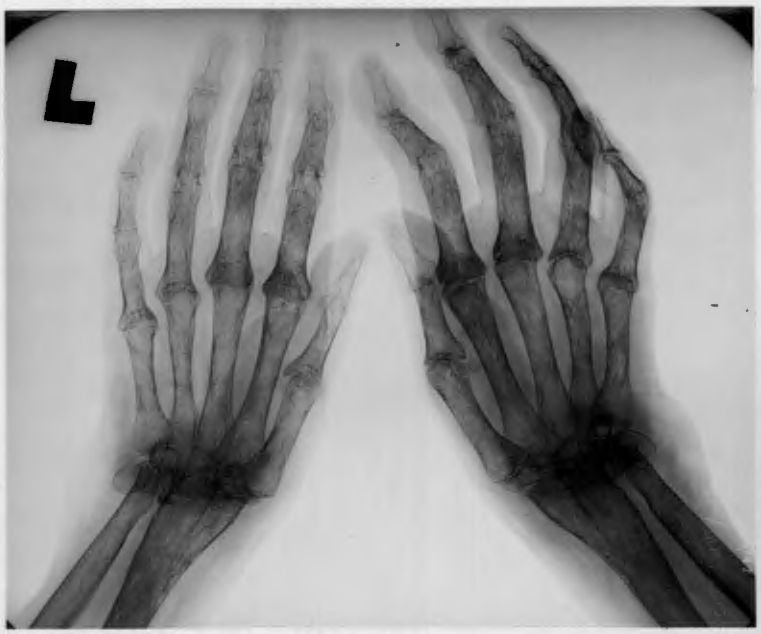


Case 2: Chronic Rheumatoid Arthritis.

Bony ankylosis of the proximal and of the terminal interphalangeal joints.
Marked destructive changes in the metacarpophalangeal joints.

FIG. 4.

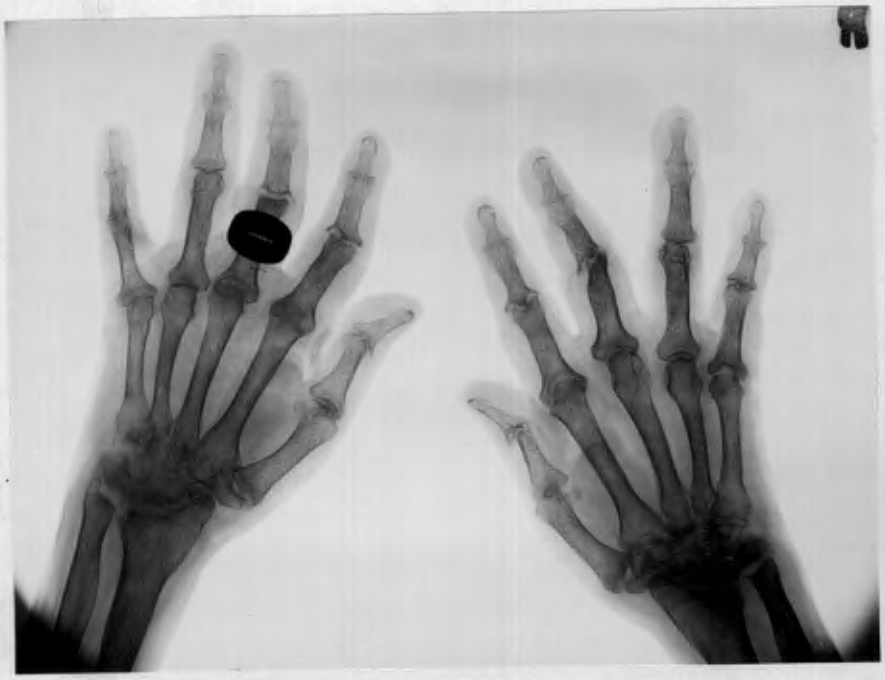
Involvement of the Terminal Interphalangeal Joints.



Case 53 : Chronic Rheumatoid Arthritis.
Bony ankylosis of the proximal interphalangeal joints and narrowing of joint spaces in some terminal interphalangeal joints.
Marked generalized osteoporosis.
Severe atrophy and ankylosis of the carpal bones.

FIG.5.

Involvement of the Terminal Interphalangeal Joints.

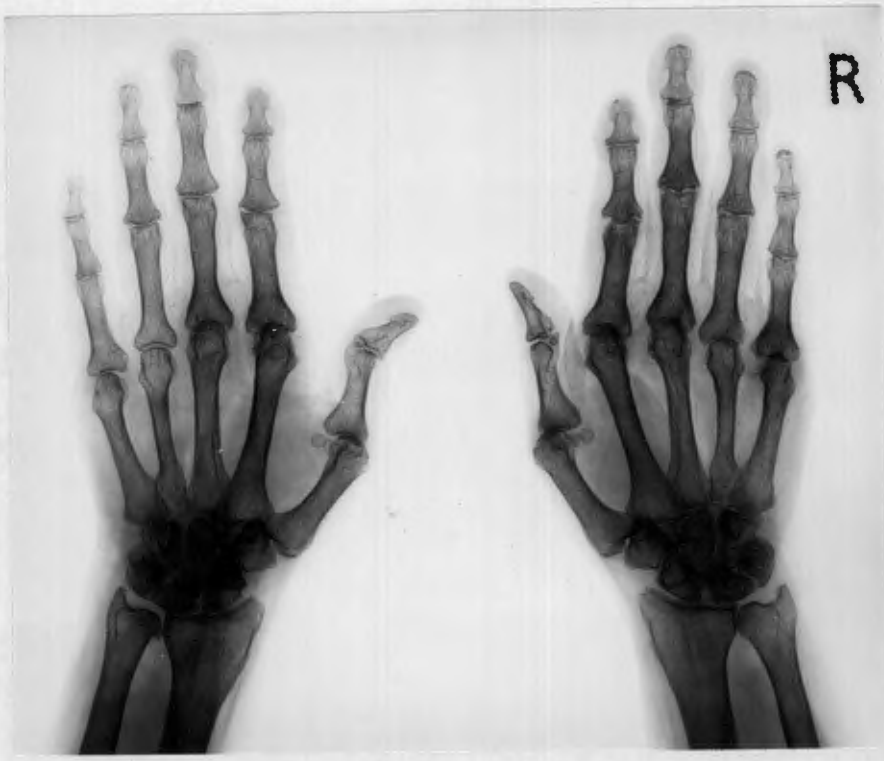


Case 3: Chronic Rheumatoid Arthritis.

Narrowing of the joint space and ankylosis of the terminal interphalangeal joints.

FIG. 6.

Involvement of the Terminal Interphalangeal Joints.



Case 61: Chronic Rheumatoid Arthritis.

Narrowing of the joint space at the terminal interphalangeal joints of the midfingers of both hands.

H. VASOMOTOR SYMPTOMS.

Vasomotor symptoms, manifested chiefly by cold, moist hands and feet, are prominent features in rheumatoid arthritis. ROPES and BAUER (1945) discussed the varied clinical manifestations of rheumatoid arthritis and stated that the vasomotor symptoms are prominent in at least two-thirds of the cases.

Many patients in this series showed subjective or objective evidence of vasomotor disturbances. Case 34 presented a difficult problem. She had suffered from attacks of Raynaud's phenomenon in her hands for several years. One year before her admission the hands felt cold more or less constantly, accompanied by very slight pain and stiffness in the fingers. Her sedimentation rate was considerably elevated but there was no objective evidence of arthritis on admission. Several months later the finger joints became swollen and tender and the diagnosis of rheumatoid arthritis became obvious for the first time.

I. EFFECT OF PREGNANCY.

COMROE (1944) and HENCH (1938) have noted the temporary ameliorating effect which often occurs when a patient with rheumatoid arthritis becomes pregnant. Unfortunately a relapse occurs a few weeks or months after the confinement.

In this series 6 of the female patients had become pregnant after the onset of the arthritis. Case 57 fell pregnant 3 times. As her arthritis did not improve with the first of these pregnancies the pregnancy was terminated. In the 2 later pregnancies (one going to full term and the other terminating in spontaneous abortion) there was complete relief of symptoms, but the pains recurred a few weeks after parturition. Case 19 had 2 pregnancies and her pains ceased temporarily, returning a few months after the confinements. Case 49 was unimproved after being pregnant for 3 months and the pregnancy was terminated. Case 54 became pregnant a month after the onset of the arthritis and there was no improvement while pregnant. Case 18 developed a slight relapse of her quiescent rheumatoid arthritis soon after falling pregnant and improved again while pregnant. Case 26 fell pregnant several times but suffered so little pain with her disease at all times that she was never aware of any changes in her condition. In 2 of the 6 cases there was thus striking, though

temporary...../

temporary, relief of symptoms while pregnant.

BARSI (1947) has treated cases of chronic rheumatoid arthritis with blood transfusions from healthy pregnant women donors in an attempt to simulate the "natural cure" which pregnancy sometimes produces in the disease. He claimed very good results in a large number of apparently "hopeless" chronic cases but his descriptions of the cases and of the results were brief.

Therapeutic measures were not specially studied in this thesis but it is of interest to record the results of the treatment of 5 of the 70 cases with transfusions from pregnant donors. Four of the cases received only a single blood transfusion of 300 cc. and one case (Case 54) received 2 blood transfusions, the second being given a month after the first. One patient (Case 27) ceased having pain a few weeks later, but had a relapse 6 months later. None of the cases showed the least objective improvement.

It would have been interesting to note the effect of this treatment on the 2 cases which improved when they were pregnant, but the opportunity was not available.

J. SEDIMENTATION RATE.

FLETCHER (1947) and COMROE (1944) stated that the sedimentation rate is almost always elevated during the active state of rheumatoid arthritis. It commonly varies from 30 to 135 mm. at the end of one hour. (Westergren's Method). However, exceptionally, it is stated that the sedimentation rate is occasionally normal in the early months of the more insidious cases. It is usually thought that as the disease subsides, the rate usually becomes slower and finally reaches normal in the inactive or "burnt-out" stage of the disease. (COMROE, 1944). The Committee of the American Rheumatism Association ("Primer on Arthritis", 1942), also considered that the rate tended to become slower as the activity of the disease subsided and that normal values were commonly observed in the "burnt-out" stages.

Table 4 indicates the sedimentation rate in 63 of the 70 cases, at the time of their initial examination.

TABLE 4./

TABLE 4.

SEDIMENTATION RATES (WESTERGREN)

AT THE END OF ONE HOUR.

S.R. (mm.)	mm. 0-8	9-15	16-30	31-45	46-60	61-75	76-90	91-105	106 +
Cases.	3	1	7	15	11	12	4	4	6

More than 50 of the patients had sedimentation rates which were raised above 30 mm. at the end of one hour. There was some relationship between the degree of elevation of the sedimentation rate and the clinical condition of the patient; the cases with very high sedimentation rates were mainly cases of very active progressive painful poly-arthritis. The sedimentation rates were repeated in 18 cases after a period varying between 6 months and one year; those cases which were improving clinically usually, but not invariably, showed a decrease in the sedimentation rate.

The findings...../

The findings in the so-called "burnt-out" cases are interesting. Clinically, a striking feature of the disease is that it may remain "active" in some cases even after very many years have passed. Cases are seen which have reached the terminal stage of contractures and ankylosis and yet they may still experience pain and swelling of the joints from time to time. Similarly, the sedimentation rate may never become normal. Cases 6, 22, 50, 57 and 67 had suffered from the disease for 43, 14, 17, 11 and 19 years respectively. Cases 6, 57, 67 still experienced slight or moderate amounts of pain periodically, but cases 22 and 50 had no pain at all, and could be regarded as "burnt-out" cases with residual deformities. Yet all 5 cases still had elevated sedimentation rates, viz.: 40 mm., 40 mm., 30 mm., 32 mm. and 64 mm respectively at the end of one hour.

On the other hand, Cases 26, 31, 46 and 51 which were clinically "burnt-out" had sedimentation rates of 15 mm., 3 mm., 5 mm. and 8 mm. respectively at the end of one hour. These findings thus tend to confirm Comroe's views (1944) but exceptions do occur in which clinically "burnt-out" cases still may have elevated sedimentation rates.

The point is of some practical importance and it indicates that orthopedic treatment of deformities and

contractures...../

contractures in the advanced cases may be undertaken even if the sedimentation rate is not within normal limits, as the rate may not return to normal even after very many years.

K. ARTHRITIS MUTILANS.

NIELSEN and SNORRASON (1946) reviewed 7 "typical cases" from the literature and then described 6 cases observed by themselves. They state that the first case was published by MARIE and LERI (1913), who termed it "Une variete rare de rhumatisme chronique: La main en Lorgnette". The changes in the hands were such that the destruction of the joints and of the bones allowed the remaining parts of the bones to slide into each other like sections of a telescope. The redundant skin was puckered with transverse folds. Radiological investigations revealed extensive decalcification and atrophy of the bones; destruction of the ends of the phalanges and heads of the metacarpals; and dislocation of the joints, producing very gross mutilating deformities.

NIELSEN and SNORRASON described 4 of their 6 cases in great detail, supplemented by clinical and radiological illustrations. All the 4 patients had suffered from chronic rheumatoid polyarthritis for very many years, (viz. 17, 50, 23 and 13 years in the 4 cases respectively), and their clinical and radiological features conformed to those described by earlier observers.

NIELSEN...../

NIELSEN and SNORRASON recognized the relationship of this condition to chronic rheumatoid arthritis, but were in favour of maintaining the "syndrome as a separate entity" on account of the gross, distinctive appearances of the cases. They acknowledged that it was not a common form of polyarthritis and stated that this was evident from the scanty attention which the "syndrome" receives in textbooks and from the small number of cases published.

Case 46 in this series has clinical and radiological features identical with those described by NIELSEN and SNORRASON, and it appears to be an indubitable case of this "syndrome". Figs 7, 8, 9, 10, 11 and 12 illustrate the clinical features of the mutilated, grossly deformed hands and feet and Figs. 13 and 14 illustrate the striking radiological changes in the hands and elbows.

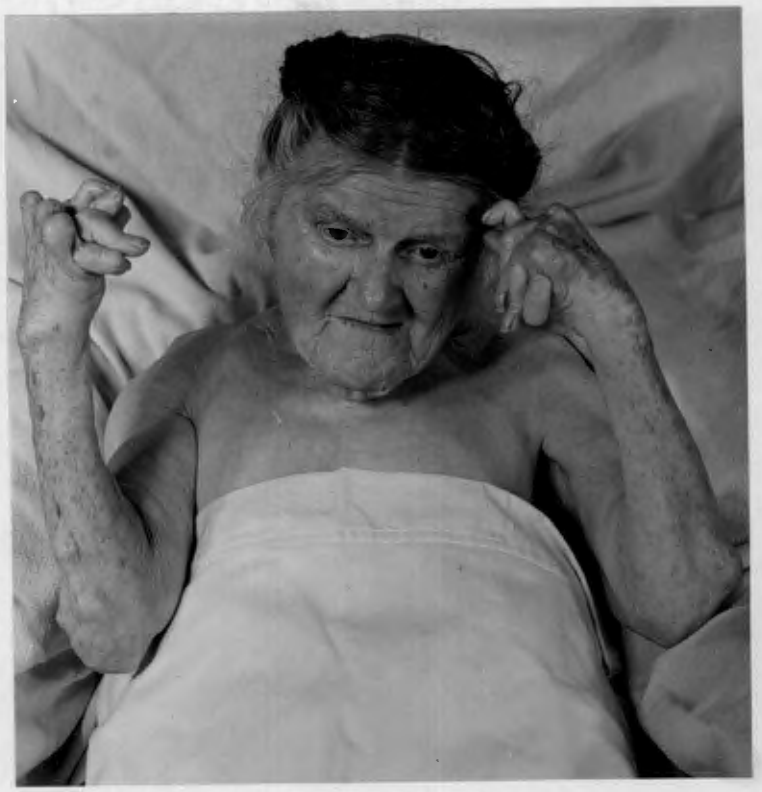
The case was an elderly European female, aged 72 who had a rheumatoid arthritis for approximately 30 years. There was no pain left and she felt quite well. The hands were grossly deformed. Many of the fingerjoints appeared to be replaced by fatty or by fibrous tissue. Some joints were subluxed and others were dislocated. Some of the phalanges were shortened on account of atrophy of the ends of the bones and the remaining parts of the bones "telescoped" into each other. The redundant skin was puckered into folds. It was hard to conceive of a grosser, more deforming or more mutilating result than was present. The wrists, elbows, knees, ankles and feet were firmly ankylosed. Multiple subcutaneous nodules

were...../

were situated over the knuckles, elbows and feet. Her general health was excellent.

FIG.7.

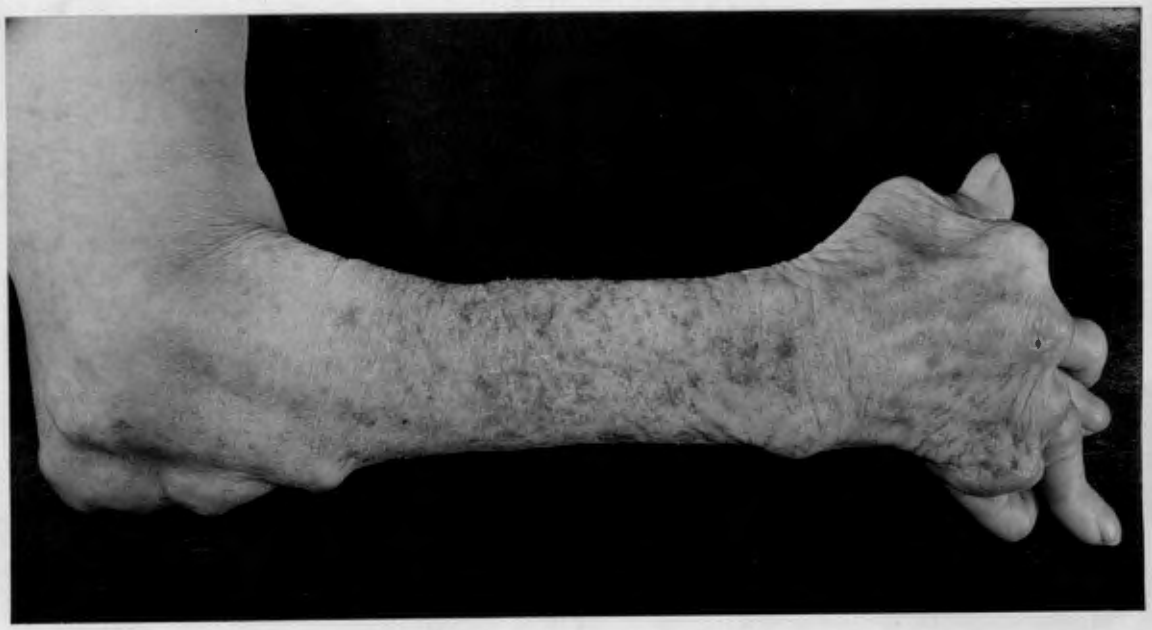
"Arthritis Mutilans".



Case 46: Gross mutilating deformity of both hands. Multiple subcutaneous nodules along ulnar border of right forearm.

FIG. 8.

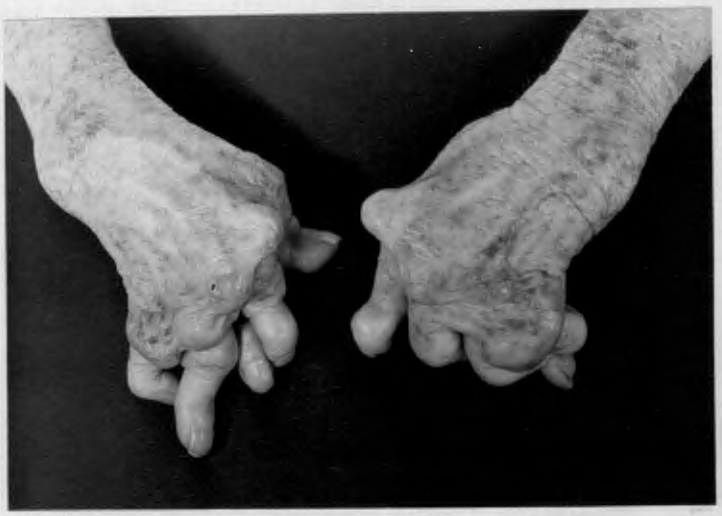
"Arthritis Mutilans".



Case 46 : Chronic Rheumatoid Arthritis.
Multiple subcutaneous nodules along ulnar border of right forearm.

FIG. 9.

"Arthritis Mutilans".

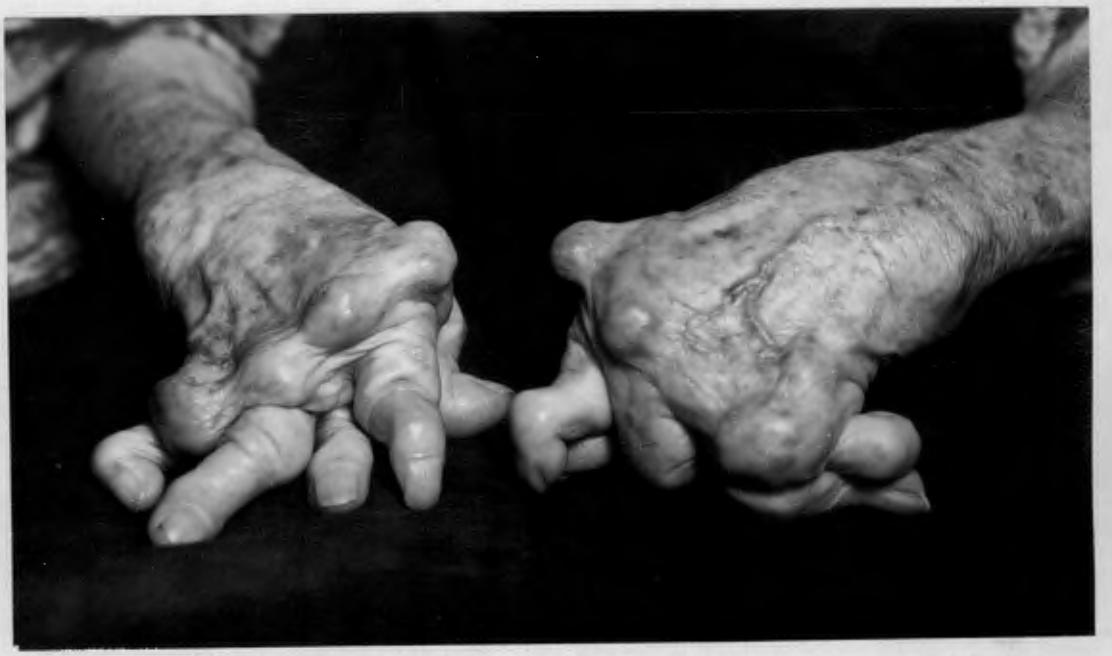


Case 46: Chronic Rheumatoid Arthritis.
Hands in their natural position.
Gross disorganization and deformity.
Subcutaneous nodules present on summits of knuckles.

(See X-Ray hands, Fig.)

FIG. 10.

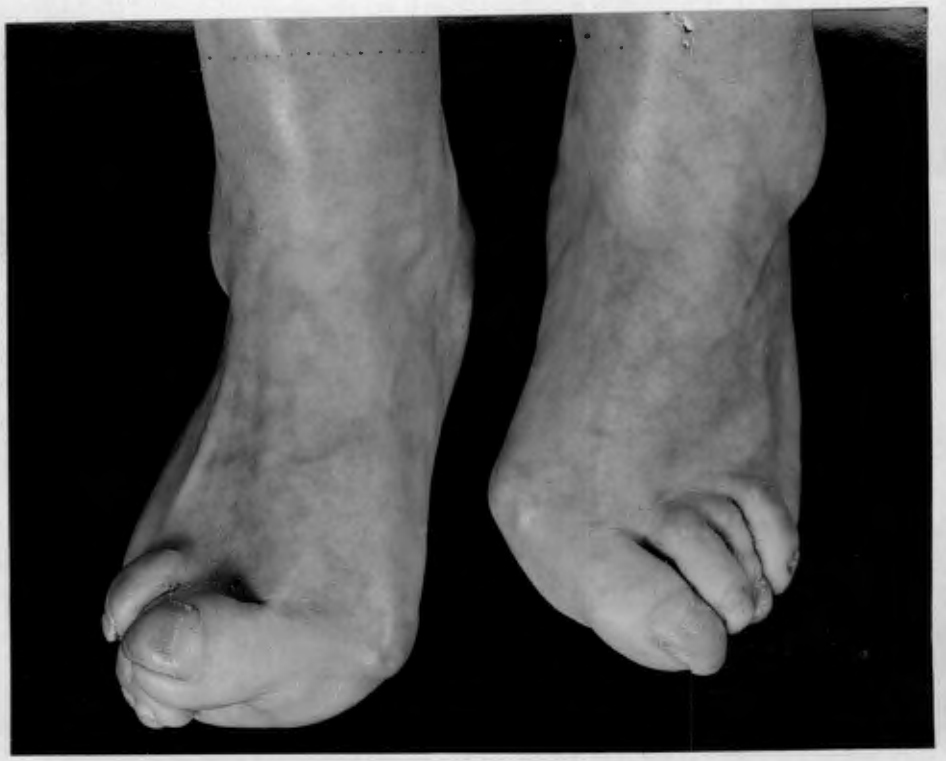
"Arthritis Mutilans".



Case 46: Chronic Rheumatoid Arthritis.
Hands with the fingers extended as much as possible.
Subcutaneous nodules on knuckles.

FIG. 11.

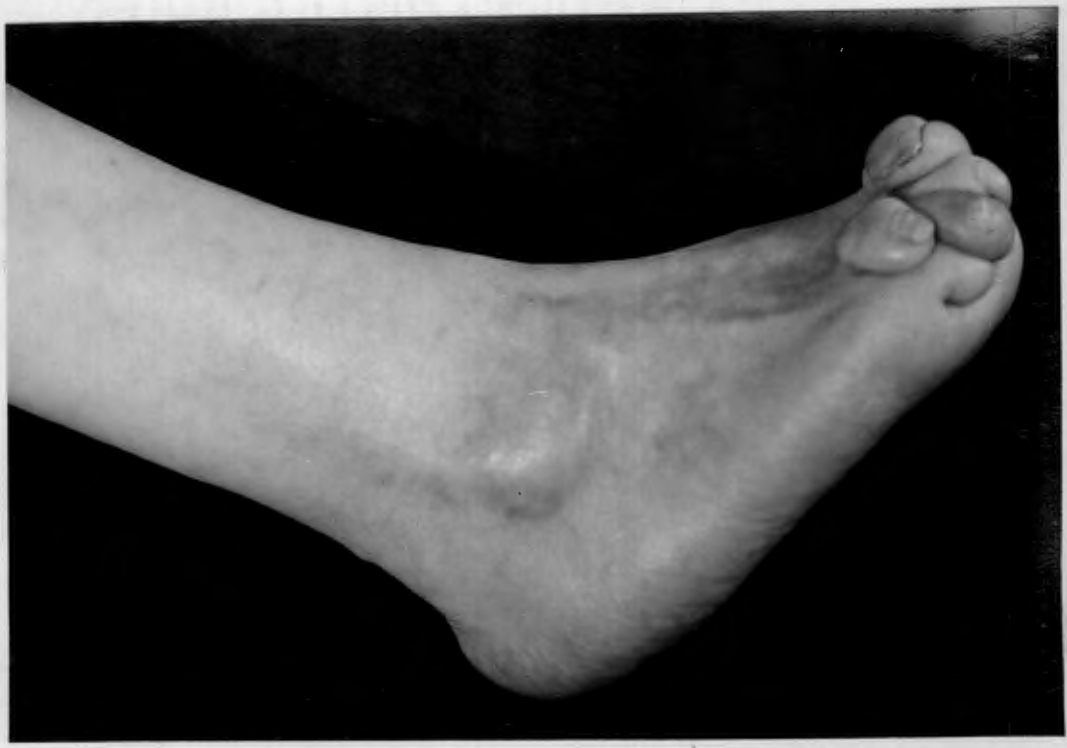
"Arthritis Mutilans".



Case 46 : Chronic Rheumatoid Arthritis.
Eversion of toes with deformity.

FIG. 12.

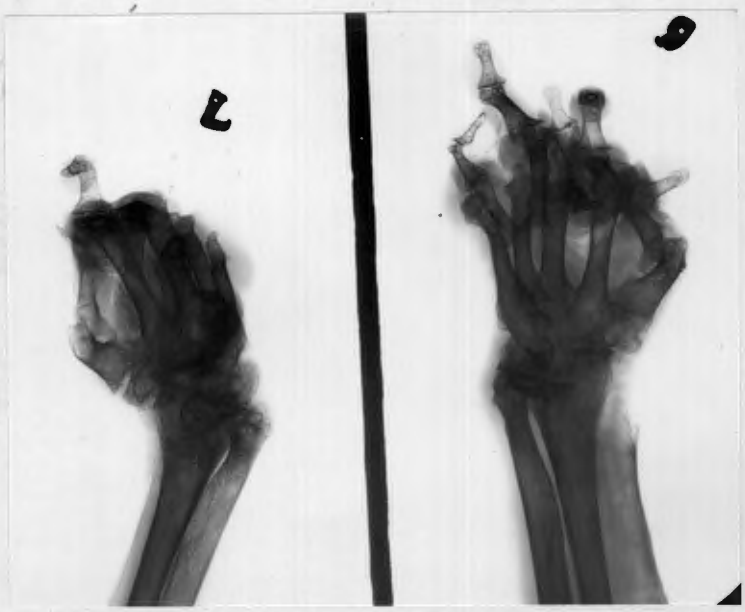
"Arthritis Mutilans".



Case 46 : Chronic Rheumatoid Arthritis.
Deformity of toes.
Nodule just detectable in tendon Achilles.

FIG. 13.

"Arthritis Mutilans".

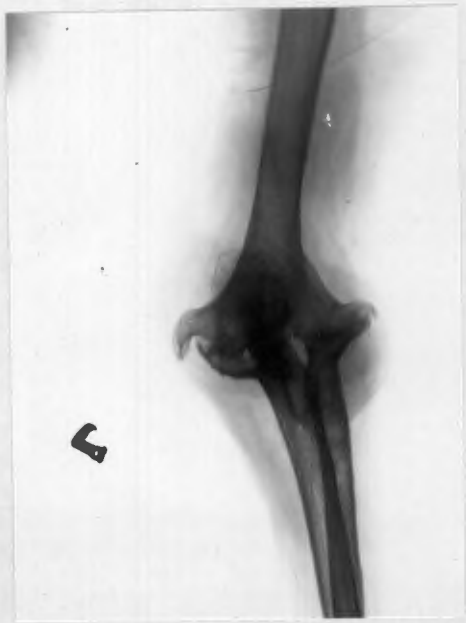


Case 46 : Chronic Rheumatoid Arthritis.

Severe atrophy of phalanges with gross disorganisation and deformity. Dislocation of joints. "Telescoping" of metacarpals and phalanges.

FIG. 14.

"Arthritis Mutilans".



Case 46: Chronic Rheumatoid Arthritis.

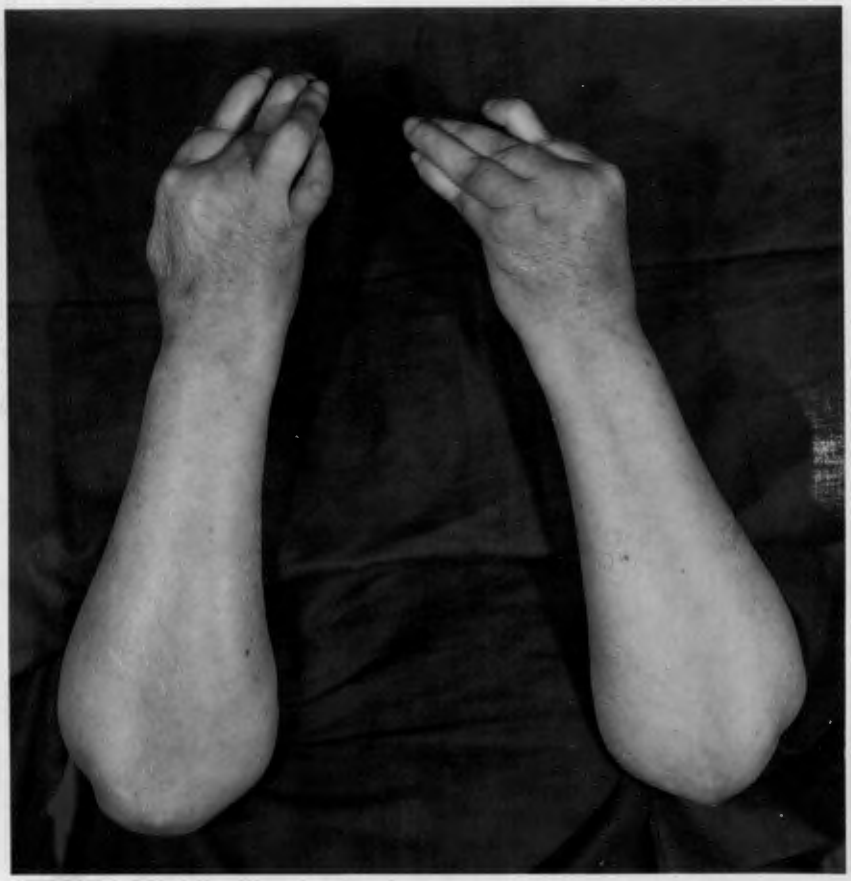
Gross atrophy of ends of humerus, radius and ulna. Destruction and deformity of elbow joint.

From a careful perusal of NIELSEN and SNORRASON's 6 cases it appears obvious that varying grades of destruction occurred in different digits. Some of the joints resemble the grosser, deforming cases of "ordinary" rheumatoid arthritis and do not show the severe destructive and mutilating changes encountered in other joints. Other cases had mutilating changes in only one or 2 joints. There is an obvious gradation of cases between "Arthritis Mutilans"; severe, deformed cases of rheumatoid arthritis with bone atrophy, subluxations, etc.; and less severe cases of rheumatoid arthritis.

In this series some cases of rheumatoid arthritis were encountered (mainly from the Conradie Home) which showed gross destructive changes in the bones and joints of the hands. These cases constitute the "link" between "Arthritis Mutilans" and other cases of chronic rheumatoid arthritis. Their features are indicated in Figs. 15, 16 17, 18, 19, 20 and 21. Fig. 21 is specially interesting as the "mutilating" changes were confined to the thumb. This case is very similar to the 2 cases in NIELSEN and SNORRASON's series which they did not describe in detail; these 2 cases also only exhibited changes in individual fingers.

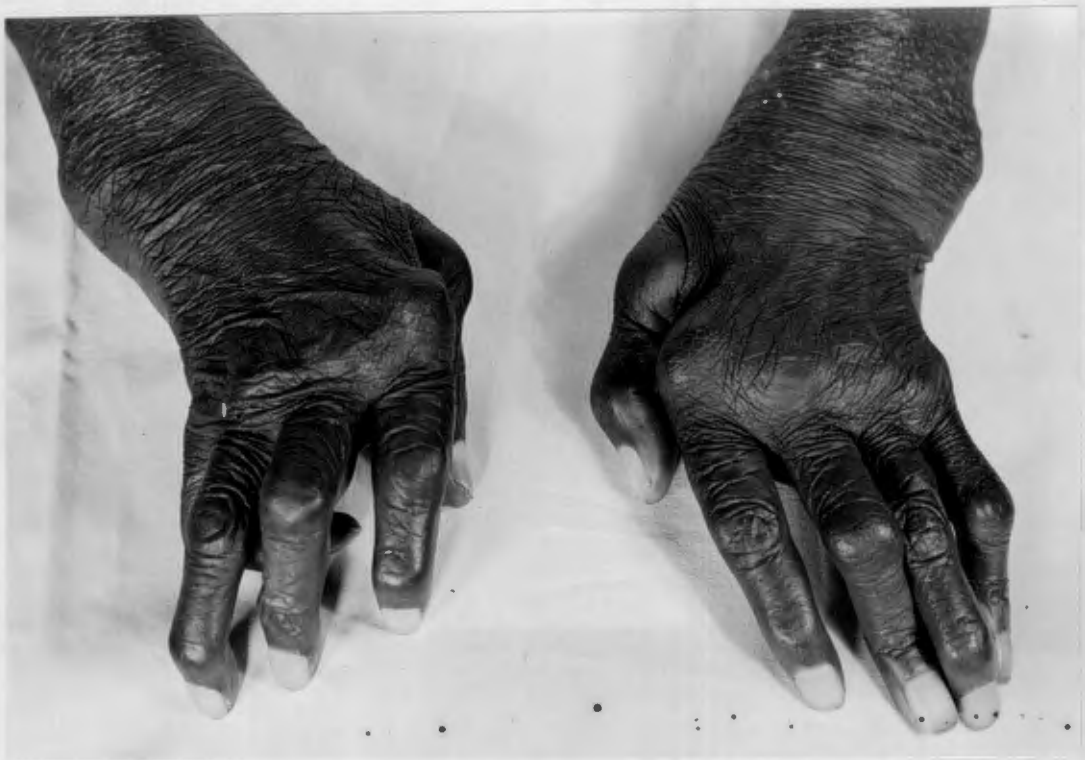
There is thus no special justification of the term "Arthritis Mutilans" as it merely indicates the grossest examples of a common condition.

FIG. 15.



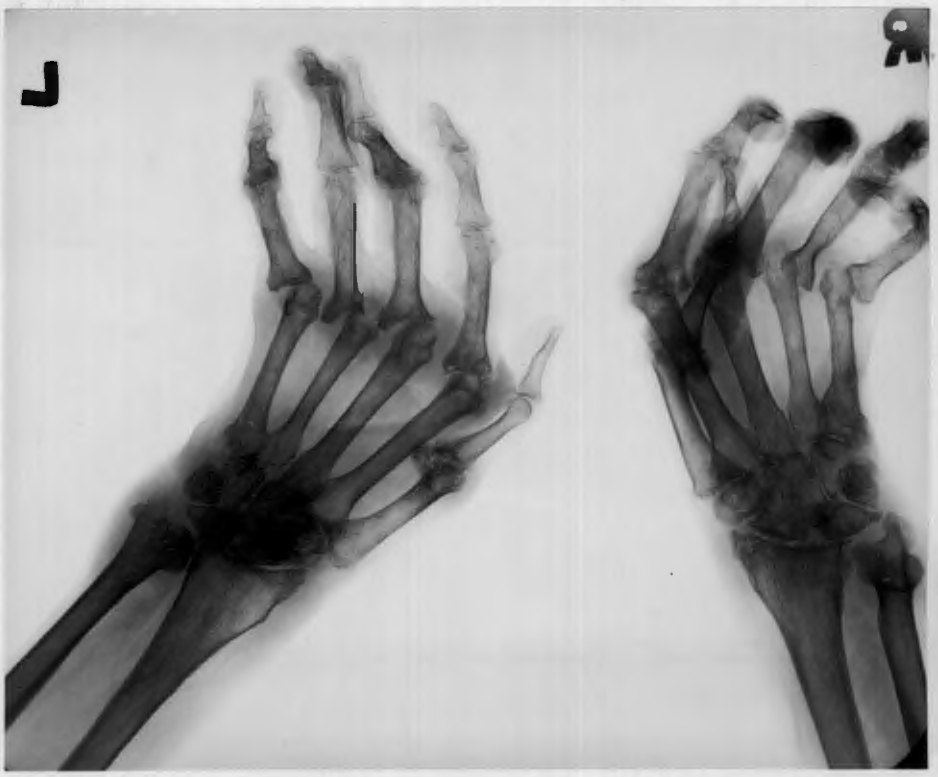
Case 62: Chronic Rheumatoid Arthritis.
Advanced case with ulnar deviation
and bizarre joint deformities.

FIG. 16



Case 67 : Chronic Rheumatoid Arthritis.
Marked ulnar deviation.
(See X-Rays, Fig. 17).

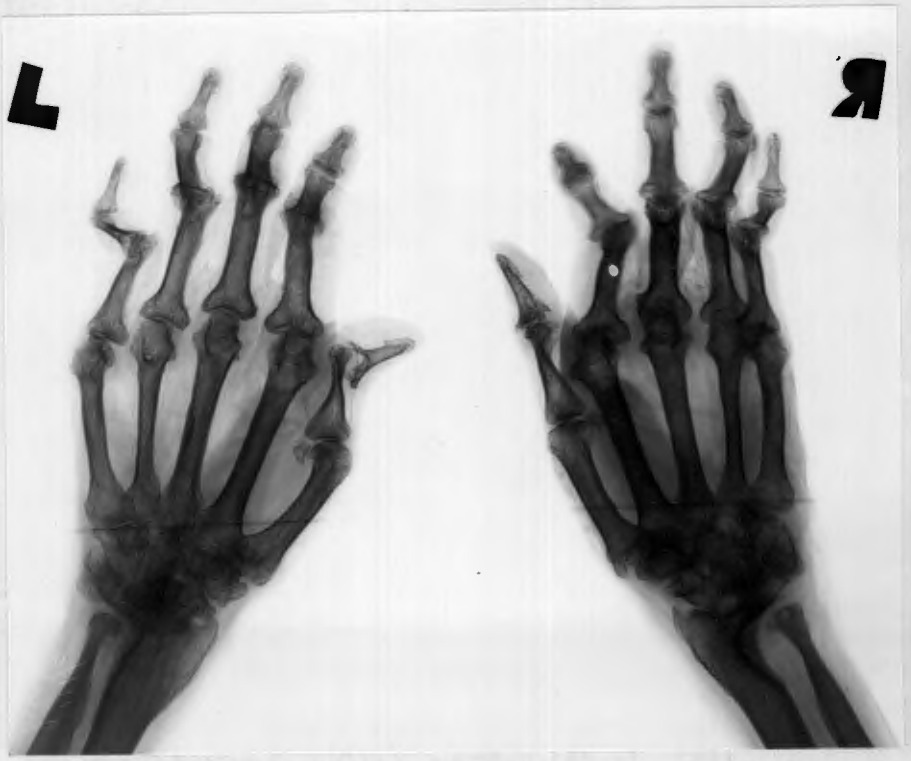
FIG. 17.



Case 67 : Chronic Rheumatoid Arthritis.

Marked deformity, ulnar deviation, and dislocations. (See Fig. 16).

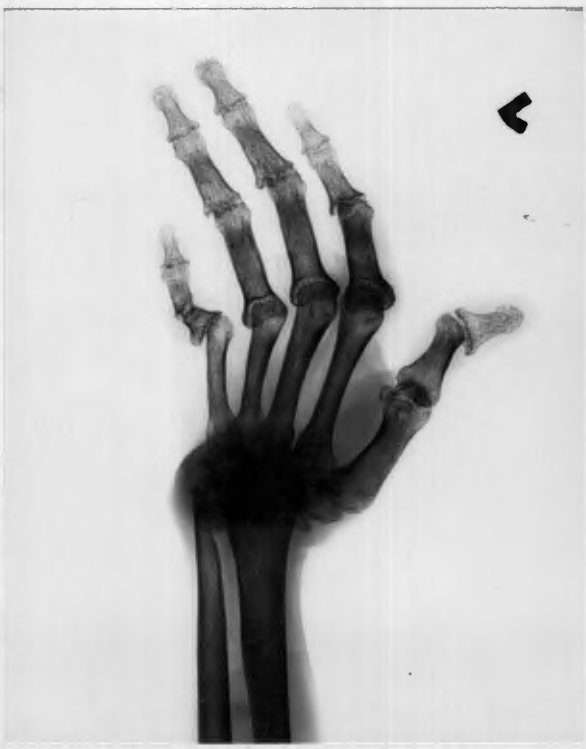
FIG. 18.



Case 64 : Chronic Rheumatoid Arthritis.

Marked atrophy of phalanges of left thumb and disorganisation of inter-phalangeal joint.

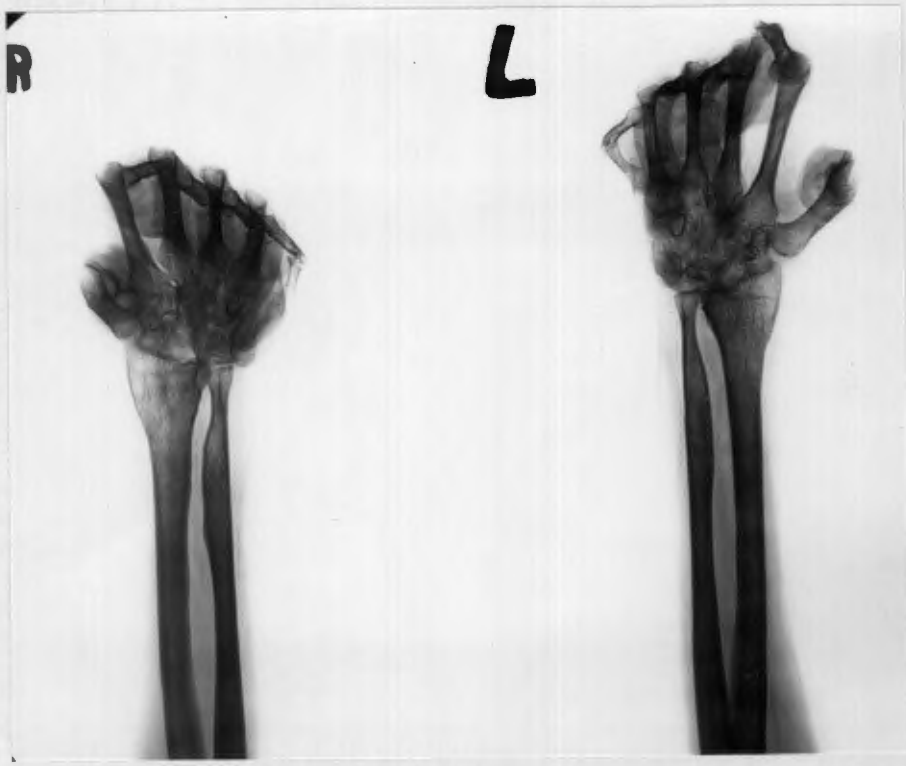
FIG. 19.



Case 16 : Chronic Rheumatoid Arthritis.

Ulnar deviation. Marked atrophy of carpus. Marked deformity fifth finger (probably due to nonunited fracture).

FIG. 20.

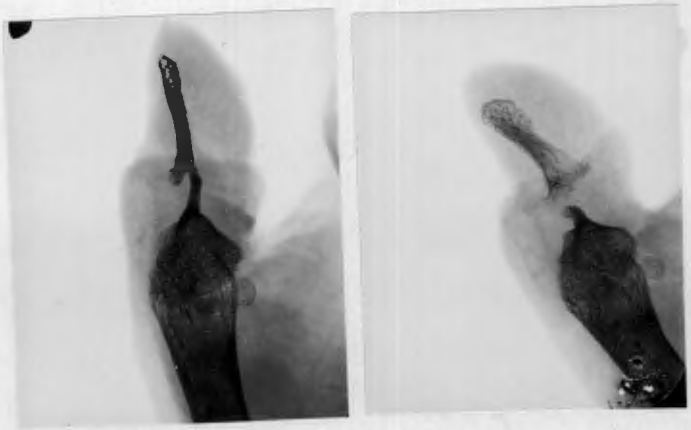


Case 35: Chronic Rheumatoid Arthritis.

(See Fig. 21 for special view of thumb).

FIG. 21.

Localised "Arthritis Mutilans".



Case 35: Chronic Rheumatoid Arthritis.
Special view of thumb (see Fig. 20).

Marked Atrophy of both phalanges with gross disorganisation of the inter-phalangeal joint.

4. RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS.

Seven cases of ankylosing spondylitis were seen while the 70 cases of chronic rheumatoid arthritis were under investigation. The relationship between the 2 conditions has always been uncertain. There are differences in the sex incidence and in the radiological features in the 2 diseases, but sufficient evidence has accumulated to indicate that there is a close relationship between them. It is well-known that cases of ankylosing spondylitis may develop arthritis of the hip and shoulder joints, and COMROE (1944) states that the disease in these regions is similar pathologically to typical rheumatoid arthritis.

POLLEY and SLOCUMB (1947a, 1947b) analysed 1035 cases of "rheumatoid spondylitis" (a synonym for MARIE-STRUMPELL'S ankylosing spondylitis). Of the 1035 cases studied, 286 had associated rheumatoid arthritis of the peripheral joints. This incidence is much higher than what one has formerly accepted, but it seems acceptable on account of the very large number of cases which were examined. They also noted that some cases commenced with initial manifestations in the peripheral joints, and that the involvement might be temporary or cause "residual damage of the peripheral joints".

Three of the 7 cases of ankylosing spondylitis

in ...../

in this series showed involvement of joints beyond the vertebral column. One, (Case 71), had the characteristic involvement of the hip, and 2 (Cases 72 and 73) had involvement of the fingers, wrists, elbows, ankles and knees which clinically was identical with the picture of rheumatoid arthritis. Case 72 had symptoms of the spondylitis for 20 years and developed the peripheral arthritis 2 years before his admission. Case 73 had the clinical features of peripheral arthritis for 8 years and the spine became painful and stiff 2 years before his admission. These 2 latter cases are thus examples of ankylosing spondylitis associated with peripheral rheumatoid arthritis. The series is very small but it is interesting to note that it includes cases which show the close relationship of the 2 diseases.

M. SKIN AND NAIL LESIONS.

1. ATROPHY OF THE SKIN.

COMROE (1944) and the Committee of the American Rheumatism Association (Primer on Arthritis, 1942) state that the skin of the extremities frequently becomes smooth, glossy and atrophic. These features were noted in many of the early and the advanced cases of rheumatoid arthritis in this series.

2. PIGMENTATION AND VITILIGO.

Pigmentary changes have been described in the skin of the face and of the extremities. They are usually described in the literature as "bronzed" in appearance. Pigmentation of the skin occurred in 7 cases in this series. In Case 44 the pigmentation affected the dorsum of the hands alone (and was accompanied by adjacent vitiliginous areas); in Cases 1 and 15 the face and the dorsum of the hands were affected, and in 4 cases (23, 24, 35 and 63), the face alone was affected. The distribution and appearance of the facial pigmentation was identical with chloasma uterini - the brownish facial pigmentation which sometimes develops in pregnancy. The texture of the skin affected by the pigmentation in all these cases was perfectly normal except over the hands in Case 15 in which the skin was thickened, dry and scaly.

Only ...../

Only 2 patients were certain of the duration of the pigmentation in their cases, viz. Cases 24 and 44. Both stated that the pigmentation developed a few months after the onset of the arthritis.

The racial incidence of the cases with pigmentation is interesting - there were 2 Europeans and 5 Non-Europeans. It is known, however, that chloasma uterinum is commoner in Non-European pregnancies than in European cases in Cape Town. Moreover, in some Non-European patients the chloasma persists permanently after the pregnancy is over. It is also known that brownish facial pigmentation, situated over the malar eminences and resembling chloasma, is not uncommon in Non-European females who have never been pregnant, and it occasionally occurs in Non-European males. Of the 5 Non-European cases with pigmentation, 4 were females.

The pigmentation of the skin has been noted in several cases but it is impossible to draw any further conclusions on its incidence in view of its frequent occurrence in non-arthritic Non-Europeans. One is not justified in concluding that Non-Europeans with rheumatoid arthritis are more liable than Europeans to develop pigmentary changes.

3. ...../

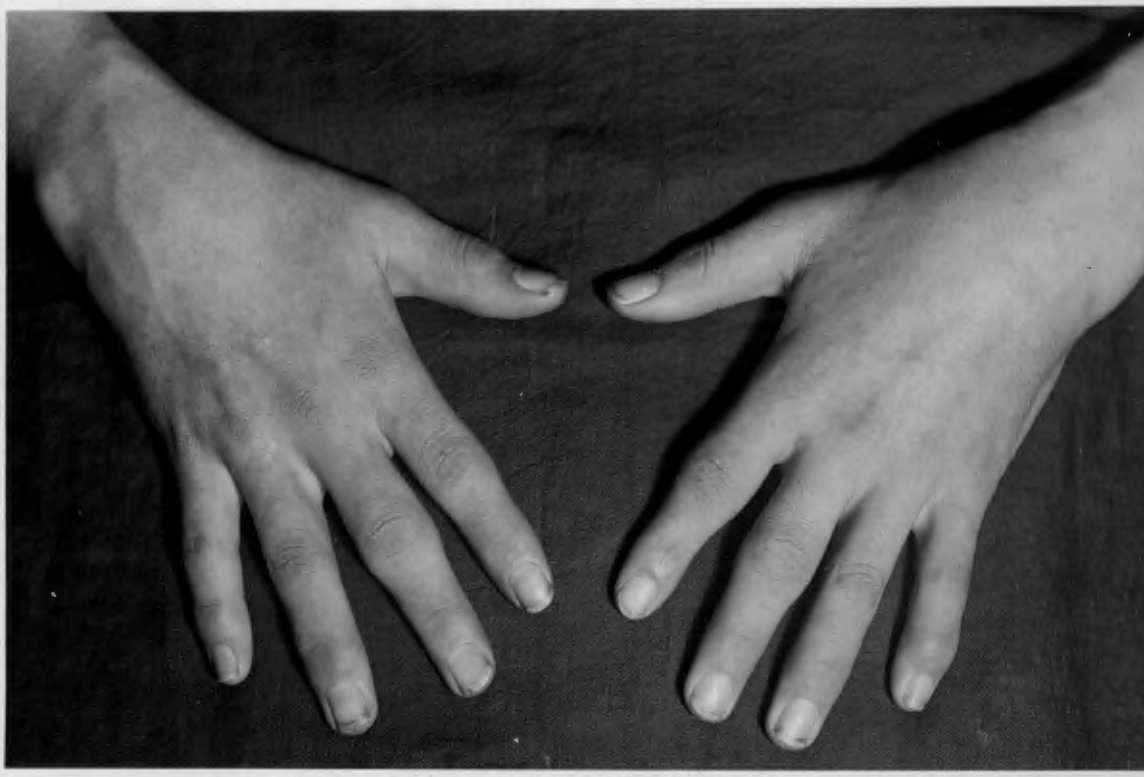
FIG. 22.

Facial Pigmentation.

Case 24 : Rheumatoid Arthritis.

Brown areas of pigmentation on the face.
(see Fig. 23.).

FIG. 23.



Case 24 : Rheumatoid Arthritis.

Fusiform swelling of proximal interphalangeal joints in case with facial pigmentation (Fig. 22.).

3. ONYCHOGRYPHOSIS.

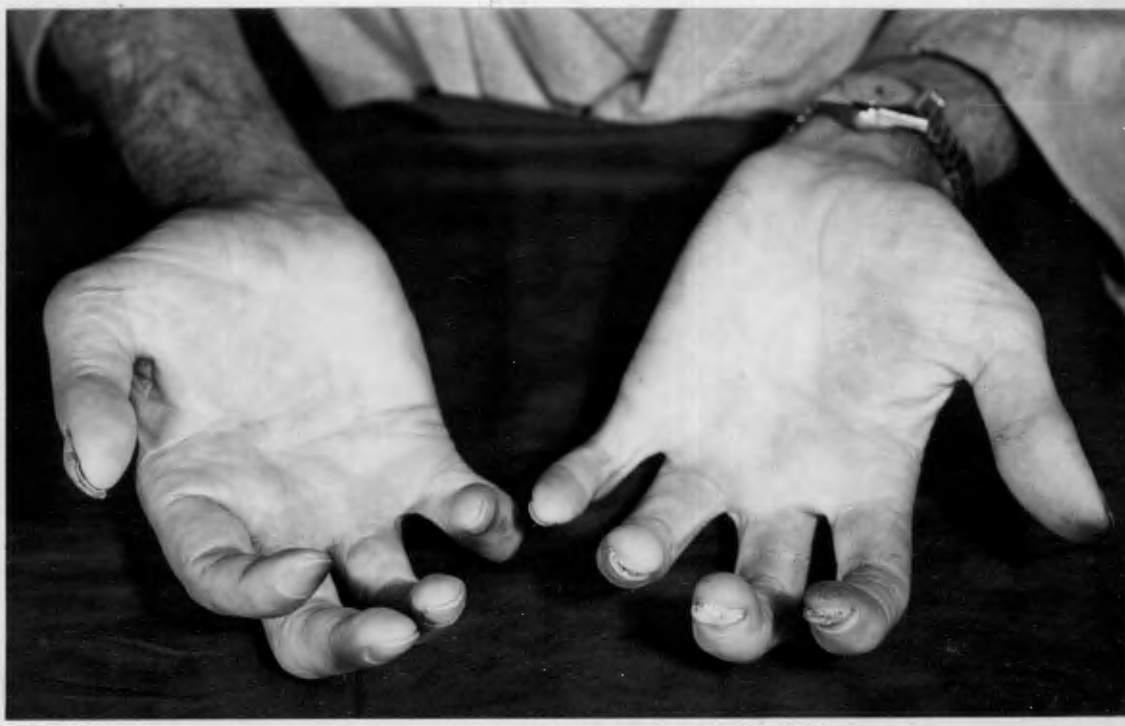
COMROE (1944) recorded a wide variety of changes which may occur in the nails in rheumatoid arthritis. The nails may become dry, brittle and may develop longtitudinal striations with or without the formation of fissures. Subungual hyperkeratosis may appear. In some cases there is a gradual separation of the nail plate from its bed, beginning at the free edge and slowly progressing towards the root (onycholysis). In some cases the entire nail may be lost. COMROE also states that in some long standing cases the nails of the toes may become elongated, raised, thickened, green or black in colour and may become twisted like a hook or a spiral with an irregular opaque surface; they may resemble the claws or horns of an animal in appearance and in texture (onychogryphosis).

Case 44 had rheumatoid arthritis for 9 months. At the onset of the disease the toenails and later the fingernails became thickened, rough and elevated. The fingernails showed the characteristic subungual hyperkeratosis elevating the nail plate (Fig. 24) and the toenails were grossly thickened and deformed (onychogryphosis) (Fig. 25). This case had varicose veins and a slight degree of varicose dermatitis and

pigmentation...../

FIG. 24.

Subungual Hyperkeratosis.

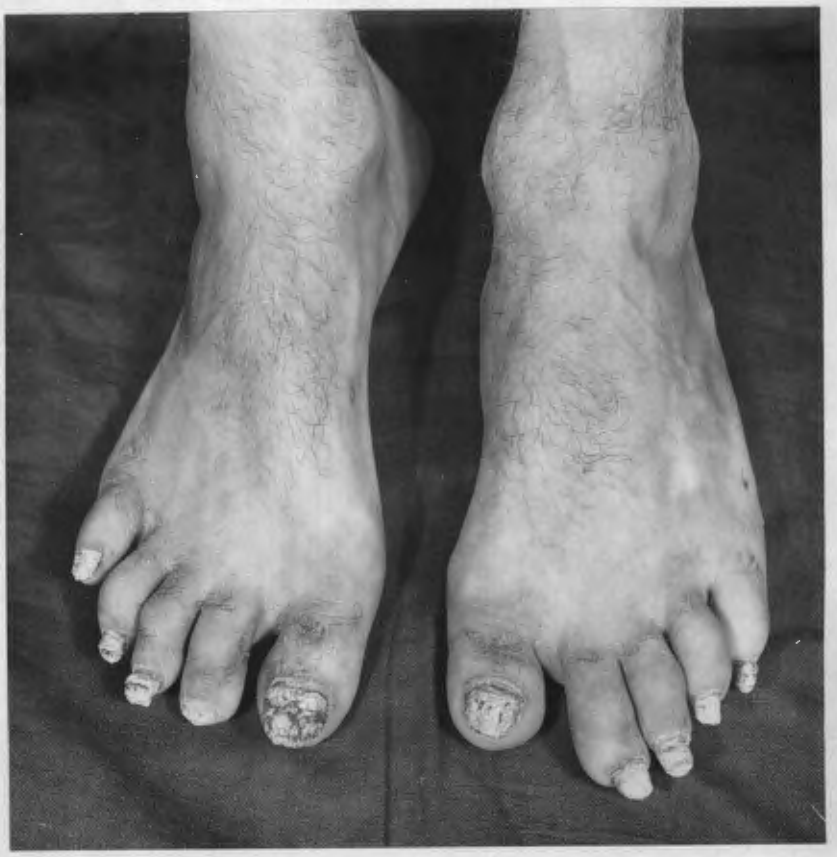


Case 44 : Rheumatoid Arthritis.

Hyperkeratosis under fingernails of left hand (See Fig. 25.).

FIG. 25.

Onychogryphosis.



Case 44 : Rheumatoid Arthritis.

Toenails thickened, rough and deformed. Shortening of left great toe due to destruction of interphalangeal joint. (See Fig. 24.).

pigmentation on the extensor surface of the legs. He was seen by a dermatologist who excluded psoriasis and fungus infection as the cause of the skin and nail changes. The interesting feature was the rapid and early development of the onychogryphosis in contrast with Comroe's opinion that it develops "in some long-standing cases".

Case 2 had a past history of onycholysis which developed 6 years ago at the time of an exacerbation of his arthritic symptoms. The nails were completely shed. New nails slowly grew out which were normal in appearance and in texture.

Case 13 with psoriatic arthritis also had changes in the nails which will be discussed later.

4. PALMAR ERYTHEMA.

PERERA (1942) noted the occurrence of palmar erythema in severe or long-standing cases of rheumatoid arthritis. Several cases had slight degrees of palmar erythema in this series but there are no examples in which it was a pronounced feature.

5. "PSORIATIC ARTHRITIS".

The association of psoriasis with rheumatoid arthritis is interesting. COMROE (1944) states that the first comprehensive study of the clinical association

of "joint...../

of "joint involvement and psoriasis" was made by BOURDILLON (1888). COMROE (1944), the Committee of the American Rheumatism Association ("Primer on Arthritis", 1942) and FLETCHER (1947) stated that psoriasis occurs in about 3 per cent of rheumatoid arthritis. In spite of some opinions to the contrary "it is generally agreed that the association between the 2 diseases is significant and not merely the coincidental occurrence of 2 rather common diseases". (Ninth Rheumatism Review, 1948). BAUER, BENNETT and ZELLER (1941) found psoriasis present in 2.7 per cent of 300 unselected cases of rheumatoid arthritis and in only 0.7 per cent of a similar number of non-arthritic controls. Similarly the presence of psoriasis is periodically mentioned in various case reports or in clinical and pathological examinations on cases of rheumatoid arthritis. FRASER (1945) for example, treated 110 cases of rheumatoid arthritis with gold and noted that 3 had psoriasis (which had been present before the onset of the arthritis.

One case of psoriasis was encountered in the series of 70 cases of rheumatoid arthritis examined (Case 13). The patient, a European male aged 70, developed psoriasis on his elbows, extensor surfaces of the forearms, buttocks, scalp, extensor surface of the legs and on the dorsal and solar surfaces of the feet. Two years later his fingers became painlessly deformed

and...../

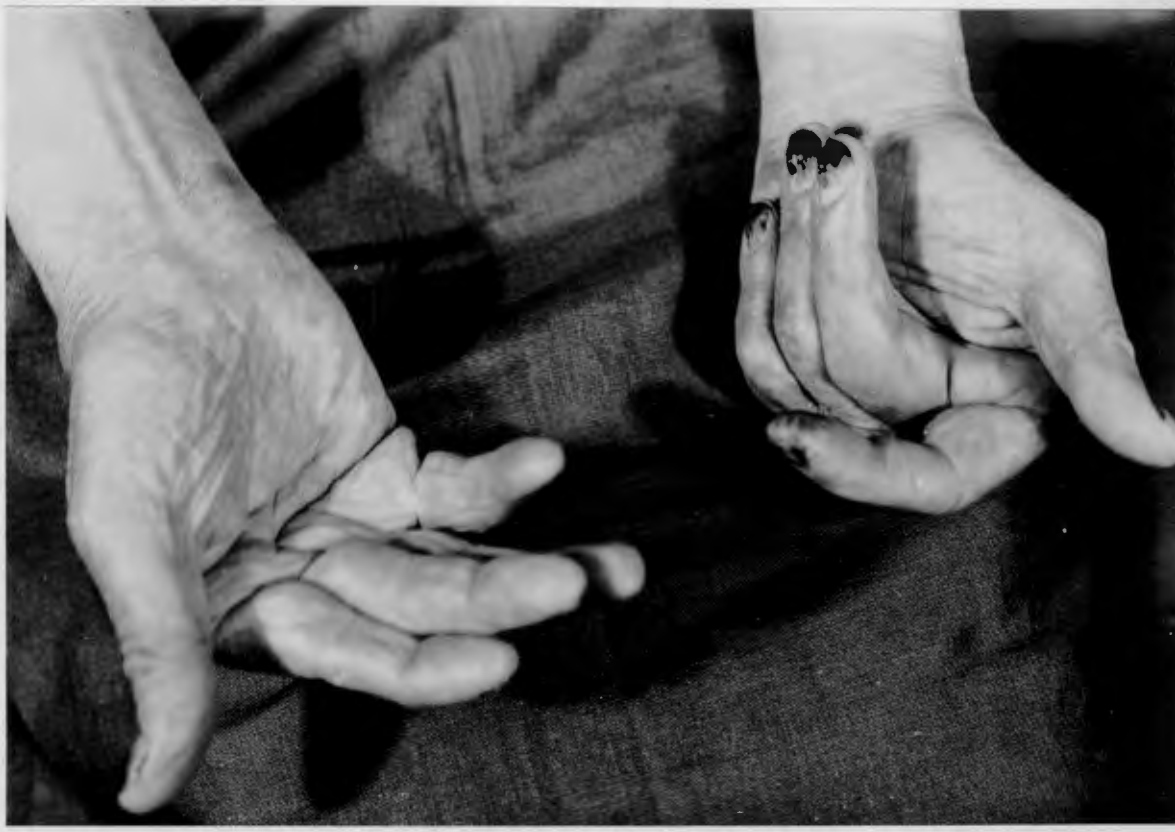
and acutely flexed at the metacarpo-phalangeal joints. Many of the interphalangeal joints, including some terminal joints, became firmly ankylosed. The toes were stiff and deformed on examination. The finger-nails had lost their shiny appearance and the surfaces were rough and dotted with tiny depressions resembling the nail changes which occur in psoriasis. The toe-nails were grossly deformed, thickened and twisted (onychogryphosis). Figs. 26 and 27 illustrate the psoriasis, the deformity of the fingers and toes and the changes in the finger and toe nails. No other joints were affected and the arthritis was completely painless.

DAWSON (1937) analysed 19 cases of rheumatoid arthritis with psoriasis. In 5 cases there were no unusual features. In 7 cases the arthritis showed no unusual features but he considered that the psoriasis was atypical with excessive "exudation" associated with translucent papules and large abundant scales". In 7 cases the psoriasis was again atypical, the rheumatoid arthritis frequently involved the terminal interphalangeal joints and the exacerbations and remissions of both diseases usually occurred simultaneously. He suggested that it might be advisable to restrict the term "Psoriatic Arthritis" to this latter group of 7

cases...../

FIG. 26.

"Psoriatic Arthritis".

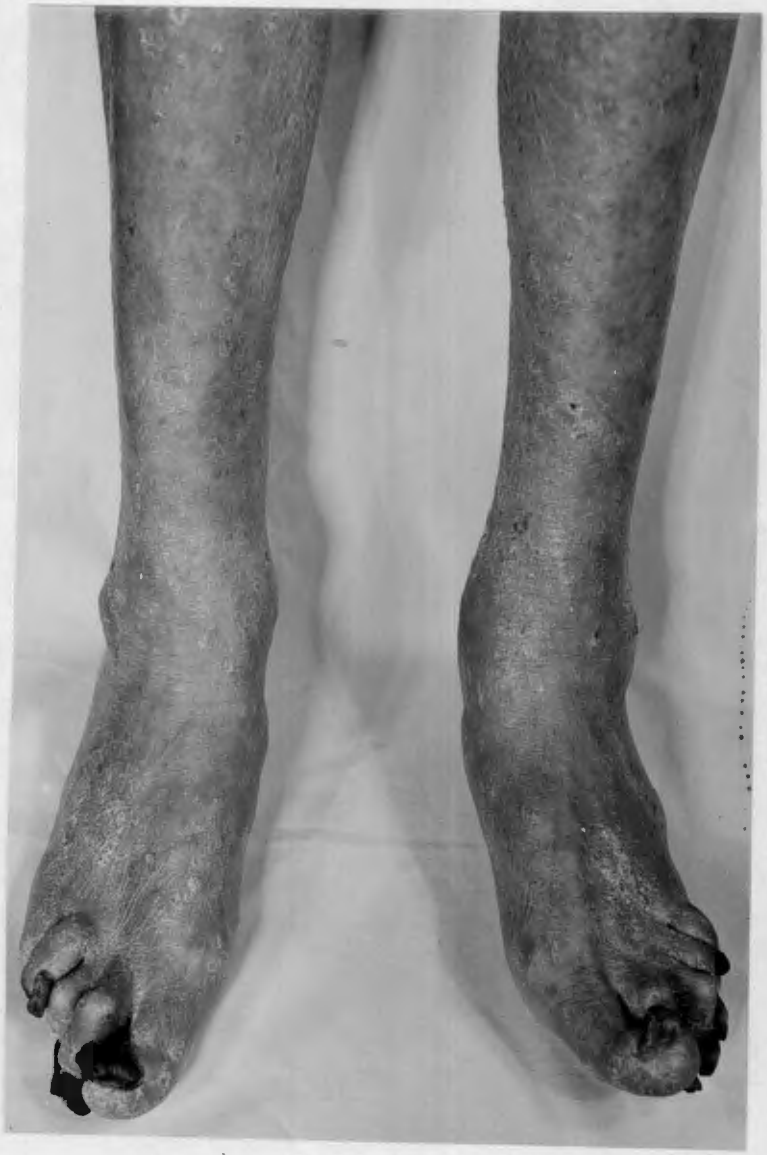


Case 13 : Rheumatoid Arthritis.

Few psoriatic scales seen on fingers. Flexion contractures at metacarpophalangeal joints. Firm ankylosis of some terminal interphalangeal joints. "Pitting" of nails obscured by black ointment. (See Fig. 27.).

FIG. 27.

"Psoriatic Arthritis".



Case 13 : Rheumatoid Arthritis.

Psoriasis on extensor surfaces of legs and feet. Eversion deformity of the toes. Toenails thickened, deformed and twisted. (Onychogryphosis). (See Fig. 26.).

cases which showed "atypical manifestations of both diseases". He also mentioned the beliefs of other observers that the term should not be so narrowly restricted and should include all cases of psoriasis and rheumatoid arthritis.

BAUER, BENNET and ZELLER (1941) analysed their findings in 23 cases of rheumatoid arthritis with psoriasis. They noted the frequent presence of nail changes in these cases. It may be that there is a higher incidence of nail involvement in cases of psoriatic arthritis than in other cases of psoriasis, but there is not enough data to draw this conclusion for certain. An interesting feature noted was the involvement of the terminal inter-phalangeal joints in 17 of their 23 cases. This tends to support the view that "psoriatic arthritis" has a special tendency to involve the terminal joints. These joints were affected in Case 13 (Fig. 26).

However, it seems inadvisable to restrict the term "psoriatic arthritis to those cases which have terminal joint involvement, as (a) many cases occur of psoriasis and rheumatoid arthritis without involvement of the terminal joints; and (b) terminal joint involvement was not uncommon in BENNET, ZELLER and BAUER's autopsy investigations (1940) in cases of rheumatoid arthritis without psoriasis and as (c) this series of 69 cases of rheumatoid arthritis (excluding Case 13 with psoriasis)...../

psoriasis) contained 13 cases with involvement of the terminal joints clinically or radiologically.

Some cases of psoriatic arthritis described in the literature had grossly deformed and disorganised joints in the hands, closely resembling the changes described above in "Arthritis Mutilans" (SCHLIONSKI and BLAKE 1936). NIELSEN and SNORRASON (1946) were aware of this point and did not include cases of "psoriatic arthritis" in their series of 6 cases of "Arthritis Mutilans". One of the cases in Bauer, Bennett and Zeller's series of 23 cases of psoriatic arthritis had marked articular destruction and bone absorption at autopsy and resembled cases of "Arthritis Mutilans". The case of "Arthritis Psoriatica" described by JURGMANN and STERN (1944) also had gross destructive and mutilating changes in the joints.

Conversely, some cases of psoriatic arthritis have mild forms of rheumatoid arthritis. KENT (personal communication, 1948), considers that the arthritis is usually less severe in the cases with psoriasis than without psoriasis. Case 13 (Figs. 26 and 27) had gross flexion deformities of the fingers and deformities of the toes, but the arthritis was painless and no other joints have, so far, been affected.

When ...../

When psoriasis and rheumatoid arthritis occur together, the psoriasis has usually preceded the arthritis, as in Case 13.

It is important to have adequate statistical data before accepting the statement that there is a special association between these 2 diseases. One of the cases of gout in this series (Case 78), e.g., developed psoriasis in the same month as he developed his first attack of gout, but it would obviously be foolhardy to suggest an association between gout and psoriasis without a great deal of careful clinical and statistical evidence. However, the majority of the reports on "psoriatic arthritis" are sufficiently numerous and convincing to enable one to conclude that the condition represents a true association, not a mere coincidence. There are no substantial differences in the features of the affected joints in cases of rheumatoid arthritis with psoriasis as compared with other cases of rheumatoid arthritis.

B. OCULAR LESIONS.

1. IRITIS.

SORSBY and GORMAZ (1946) have given a full description of iritis in "rheumatic affections", including rheumatoid arthritis. He observed iritis 15 times in 332 patients with rheumatoid arthritis. Iritis is well-known as an occasional accompaniment of gonococcal arthritis and of "Reiter's Syndrome" (HOLLANDER et al, 1945), and SORSBY and GORMAZ have clearly shown that it also occurs in a small percentage of cases of rheumatoid arthritis. SHORT (1947) encountered iritis, or a history of it, in 3 per cent of 132 consecutive cases of rheumatoid arthritis.

Four cases in the series of 70 cases of rheumatoid arthritis had iritis. This incidence corresponds closely with the figures obtained by SORSBY and GORMAZ (1946). In Case 2, the iritis developed at about the same time as the onset of the rheumatoid arthritis 23 years previously. Residual synechiae were detectable on examination. Case 67 developed iritis 2 years ago, 9 years after the onset of the rheumatoid arthritis and the eyes were still painful. Cases 36 and 38 had an interesting feature in the history of their iritis.

Case 36 ...../

Case 36 suffered from recurrent attacks of acute iritis which developed every October month for the past 10 years: he has suffered from severe rheumatoid arthritis for the past 2 years and had improved considerably at the time of examination. Case 38 suffered from recurrent attacks of iritis which developed every March or April for the past 8 years; he has suffered from a mild form of chronic rheumatoid arthritis for 3½ years. The problem became more interesting when a brother of Case 36 was examined. This patient, (Case 74) had ankylosing spondylitis without rheumatoid arthritis - and he also suffered from cyclic attacks of iritis! BUCKLEY (1945) stated that "iritis" is noted in about 10 per cent of cases of ankylosing spondylitis, and SORSBY and GORMAZ (1946) observed iritis 3 times in 53 patients with ankylosing spondylitis.

The cyclic nature of the occurrence of the iritis in these cases suggested the possibility that it was due to allergy. Arthritis is frequently present in certain "allergic" disturbances (such as serum-sickness and polyarteritis nodosa), and it is interesting to note that iritis, probably allergic in origin, preceded the development of rheumatoid arthritis in 2 of these cases.

2. SCLEROMALACIA...../

2. SCLEROMALACIA PERFORANS.

FLETCHER (1947) and COMROE (1944) have reviewed several accounts of this unusual condition. More than two-thirds of the few cases which had been recorded occurred in patients with rheumatoid arthritis. The chief finding is the appearance of defects in the scleras which may coalesce so that large gaps may appear in the scleras in which the area lies uncovered or only partially covered by conjunctiva.

The microscopic findings in the scleras markedly resembled the structure of the subcutaneous nodules found in rheumatoid arthritis, VERHOEF and KING (1938). FINGERMAN and ANDRUS (1943) noted the occurrence of this ocular lesion in 2 of their 61 autopsied cases of rheumatoid arthritis.

It is interesting to note the occurrence of nodules in the scleras, as RAVEN, WEBER and PRICE (1948) have described a fatal cause of rheumatoid arthritis with a generalised distribution of nodules in the subcutaneous tissue, pericardium, endocardium, pleurae, lungs and larynx.

3. SJÖGREN'S SYNDROME.

WEBER (1947) has given a full description of "Sjögren's Syndrome". In its complete form it includes keratoconjunctivitis sicca, rhinitis sicca, pharyngitis sicca, laryngitis sicca and xerostomia, but it is far more often incomplete. There are chronic inflammatory changes in the parotid glands, usually without suppuration, but with recurrent exacerbations, leading to permanent enlargement and sclerosis. The clinical onset is intermittent and insidious and the patients are mostly middle-aged women. WEBER (1947) stated that "arthritis symptoms" may be present, and SORSBY and GORMAZ (1946) in their review of the literature on ocular lesions in rheumatoid arthritis noted that "rheumatoid arthritis seems to be part of the Sjögren Syndrome".

4. "BAND-SHAPED OPACITY OF THE CORNEA".

SORSBY and GORMAZ (1946) stated that there is a growing and substantial literature on the occurrence of irideocyclitis with a peculiar band-shaped opacity of the cornea in cases of rheumatoid arthritis in children. The condition is also briefly discussed in the "Ninth Rheumatism Review" (1948) and the reviewer mentioned 24 children with this corneal lesion, 19 of whom had rheumatoid arthritis.

.. ..

There were no signs of Scleromalacia Perforans, Sjögren's Syndrome or "Band-shaped Opacity of the Cornea" in any of these cases, but the patients were not examined by opthalmological specialists and no special methods of ocular examination were performed.

0. LYMPHADENOPATHY and SPLENOMEGALY.

The association of rheumatoid arthritis with lymphadenopathy and splenomegaly has resulted in the creation of "new syndromes" such as "Still's Disease" and "Felty's Syndrome".

STILL's original article written in 1897 was reproduced in 1941. STILL noted the occurrence in children of cases of rheumatoid arthritis which had clinical features identical with those seen in adult cases. He also noted cases of rheumatoid arthritis in children associated with generalized adenopathy and splenomegaly and considered that these cases presented "such marked differences as to suggest that they have a distinct pathology". Since then cases of rheumatoid arthritis in children associated with lymphadenopathy and splenomegaly have been known as "Still's Disease".

It is interesting to review STILL's reasons for suggesting that the condition which now bears his name was a separate entity. He stated 5 reasons which led him to make this suggestion:

1. The joints had an "absence of bony lipping and grating, even after the disease has lasted some years". He considered this to be very unlike the "bony enlargement of the joints found in advanced rheumatoid arthritis". This point was not acceptable as many joints affected by rheumatoid arthritis never show secondary osteoarthritic changes.

2. ...../

2. Pathologically, at autopsy, the joints "show marked differences". "In the children's disease there is complete absence, even in advanced cases, of cartilaginous changes which are seen quite early in rheumatoid arthritis of adults." However the articular cartilage may not be affected in some cases of adult rheumatoid arthritis in their earlier stages.

3. He considered the adenopathy the most important point of distinction clinically between "this disease and rheumatoid arthritis". He wrote: "It is, as far as I know, never found in rheumatoid arthritis of adults whereas it is constant in the disease here described".

4. Splenomegaly was another important distinction; he believed that it was unknown in adult cases.

5. There was "a liability to serous membrane inflammation in these cases" - "a liability which is not shared by rheumatoid arthritis of adults".

It can be seen therefore that STILL was not aware of the occurrence of adenopathy and splenomegaly in some of the cases of adult rheumatoid arthritis. As an addendum to his article, however, he noted that "since" the above paper was written CHAUFFARD and RAMOND (1896) have described occasional enlargement of glands in adults with an acute form of rheumatoid arthritis".

Most reviewers of the subject have found no justification for the retention of the term "Still's Disease as it is now well-known that some adult cases of rheumatoid arthritis may have adenopathy and

splenomegaly...../

splenomegaly. COSS (1946) for example, stated that "at present Still's Disease is considered to be simply rheumatoid arthritis occurring in young persons" and that the apparent differences were due merely to the varying effect of the disease processes in youth and in maturity. Subsequent events, too, have proved the inaccuracy of Still's fifth reason for suggesting that the condition described was a separate entity.

The youngest case in this series was Case 59, aged 9 years, with splenomegaly and generalized adenopathy. She had rheumatoid arthritis since the age of 2 years.

.. ..

FELTY (1924) observed a case of chronic polyarthritis associated with slight splenomegaly and leucopenia. He considered the association of all 3 features to be unusual and "searched the hospital records for similar pictures". This search at once introduced a possible source of error as the author was engaged in compiling and collecting cases of a <u>particular type</u> and was not studying them with a wider group of cases of polyarthritis.

FELTY (1924) thus collected 5 cases of chronic polyarthritis, splenomegaly and leucopenia. Three of these cases had slight adenopathy. Brownish pigmentation of the dorsum of the hands or of other exposed parts was noted in all 5 cases. The total leucocyte counts were 2,680, 1,000, 2,720, 2,080 and 4,200. The combination of rheumatoid arthritis, splenomegaly and

leucopenia...../

leucopenia thus became known as "Felty's Syndrome".

FELTY considered that it was unlikely that his cases were merely the confusion of 2 separate clinical entities occurring coincidently, and considered that the features "were manifestations of one pathological process". He added that he was "more or less forced to the conclusion that the syndrome is a distinct clinical entity".

Many papers were subsequently published on "Felty's Syndrome". The concept of the condition as a distinct entity must have been acceptable to some as WEBER (1937) presented a case of "Felty's Syndrome" at the Proceedings of the Royal Society of Medicine. The case had polyarthritis with a moderate degree of generalised adenopathy and a slight splenomegaly - but had no leucopenia. Yet WEBER presented it as a case of "Felty's Syndrome".

Splenectomy has been performed in 3 cases of rheumatoid arthritis with splenomegaly by BACH and SAVAGE (1940). They claimed that the cases improved to a moderate or marked extent clinically. This improvement is difficult to understand as the histology of 2 of the removed spleens showed the presence of amyloidosis! On reading the case reports there is little to support the author's claims, and HENCH (1941 stated that he "would hardly call the improvement in

the cases...../

the cases marked" and that he did not advise splenectomy in the treatment of rheumatoid arthritis.

FINGERMAN and ANDRUS (1943), CURTIS and POLLARD (1940) and other workers suggested that "Felty's Syndrome" is not a clinical entity and that it is merely one particular symptom complex of rheumatoid arthritis and that it occurred merely as a matter of chance. HATCH (1945) reviewed fully all the previously reported cases that contained reports by pathologists. He concluded that chronic rheumatoid arthritis with splenomegaly and leucopenia did not constitute a distinct clinical syndrome. In 4 of the 15 cases which he reviewed there was an obvious cause of the splenomegaly, e.g. amyloidosis, miliary tuberculosis, etc.

The conclusion which the majority of investigators have accepted is that there is no justification for the use of the term "Felty's Syndrome" as, in some cases the splenomegaly and leucopenia are due to an associated disease. In other cases the findings are due to an association of rheumatoid arthritis with 2 known accompaniments of the disease which may be absent, occur singly or occur together.

As it is known that diseases with chronic splenomegaly may have leucopenia (e.g. Banti's Syndrome, Gaucher's Disease) a third possible explanation is that it is the splenomegaly which is responsible for the leucopenia in some cases of "Felty's Syndrome".

The presence...../

The presence or absence of lymphadenopathy and splenomegaly was carefully noted in this series of cases. Splenomegaly was observed in 7 of the 70 cases - an incidence of 10%. This is in keeping with the generally accepted view that splenomegaly occurs in 5 - 10 per cent of cases (Primer on Arthritis, 1942). The degree of enlargement was slight in all 7 cases and the spleen extended 1 - 2 fingerbreadths down below the left costal margin. In assessing whether a patient has lymphodenopathy or not, there are very great practical difficulties which are seldom mentioned by writers when they record the results of their findings in cases of rheumatoid arthritis and in other diseases. Normally, for example, there may be slight or moderate enlargement of inguinal glands in healthy people, and the submandibular glands are clinically enlarged in a fair percentage. It is difficult to be certain whether glands in these sites have any significance unless they are very large. Thus the presence of glands in these sites were noted but were not included in the results unless they were very large or unless they formed part of a generalised adenopathy.

Generalised lymphadenopathy of the axillary, cervical, epitrochlear and inguinal glands were noted in 7 cases. The axillary glands were enlarged in 8 cases; the epitrochlear glands in 4 cases and both axillary and epitrochlear glands in one case. The size

of the...../

of the glandular enlargement varied from 1 cm. to 1" in diameter in the various cases; glands smaller than 1 cm. in diameter were not included. There are obviously many fallacies in these conclusions - the same fallacies that exist whenever the extent or degree of adenopathy is described unless the enlargement is of some magnitude.

The leucocyte count in 57 cases varied between 3,700 per cu. mm. and 17,250. In 5 cases, the total leucocyte count was 5,000 per cu. mm. or less and in 11 cases the leucocyte count was over 12,000 per cu. mm. In the remainder of the cases the leucocyte count was within normal limits. It is usually stated that "the white cell count varies considerably in different cases. In the majority of instances it is within normal limits or only slightly elevated. In the acute and active stages, however, counts of 12,000 to 20,000 may be observed, while in long-standing chronic cases a definite leucopenia often develops". (Primer on Arthritis, 1942).

In only one instance (Case 62) was there an association of splenomegaly and leucopenia (3,700 per cu. mm.) No obvious cause other than rheumatoid arthritis could be detected to explain the presence of these findings. The haematological investigations are indicated in Table 5.

This series thus clearly indicates the inherent fallacy of grouping certain features of a widespread

disease...../

disease like rheumatoid arthritis into separate compartments such as "Felty's Syndrome". There were 7 cases with splenomegaly and 5 with leucopenia, but in only one instance were these features combined. In other words it appears that splenomegaly occurs in 5 - 10 per cent of cases of rheumatoid arthritis; leucopenia occurs in a smaller percentage and, at times, both features may be present in the same case, constituting an example of so-called "Felty's Syndrome". With regard to the pigmentation of the skin which FELTY noted in his 5 cases, it has already been noted that 7 cases in this series had pigmentation, but these were not the same cases which had splenomegaly.

TABLE 5.

Haematological Features of a Case of "Felty's Syndrome".								
Case	W.B.C.	P.	L.	M.	E.	Hb.(G).	R.B.C.	V.P.C.
62	3,700	55	43	2	-	11	3.6	35

P. "TUBERCULOUS RHEUMATISM".

During the radiological examination of the heart in this series of cases, 2 instances of pulmonary tuberculosis were encountered(Cases 9 and 13). The sputa contained tubercle bacilli. Case 9 was a typical case of chronic rheumatoid arthritis with a subcutaneous nodule over the elbows (Fig. 28). Case 13 had rheumatoid arthritis with psoriasis and has been discussed above. It was not possible to determine the exact duration of the lung lesions in the 2 cases.

The suggestion that tuberculosis can produce not only the characteristic, accepted type of tuberculous arthritis (which is usually a mono-arthritis with direct invasion by tubercle bacilli) but also an acute or chronic polyarthritis resembling rheumatic fever or rheumatoid arthritis was introduced by PONCET (1902). This latter condition is sometimes known as "Tuberculous Rheumatism" or as "Poncet's Disease". This concept has not found favour in the United States (BRAV and HENCH, 1934).

MONTUSCHI (1944) described a case of bilateral pleural effusion followed by an acute febrile polyarthritis which was temporary. Tubercle bacilli were never found in the sputum and no definite

radiological ...../

radiological evidence of pulmonary tuberculosis could be detected. Although it is admitted that it is impossible to prove the tuberculous etiology of most cases of so-called "idiopathic" pleural effusion, the fact remains that Montuschi was unable to produce evidence of a tuberculous etiology. In his differential diagnosis, he too readily excluded rheumatic fever which is known to be able to cause pleurisy and did not consider the possibility of a visceral angeitis.

KLING and LEVINE (1941) reported a case of pulmonary tuberculosis which developed chronic arthritis of a knee and subacute arthritis of several other joints. Synovectomy was done and miliary tubercles and tubercle bacilli were found in the synovial membrane. However, as the Editor noted, "this case is one of tuberculous polyarthritis and does not support the conception of Tuberculous Rheumatism" (Ninth American Review, 1948).

SHELDON (1946) described 6 cases of "Tuberculous Rheumatism". In one case there was merely arthralgia; 4 cases had the features of an acute or subacute polyarthritis, somewhat resembling rheumatic fever and only one case had chronic rheumatoid arthritis. He suggested that the entity deserves closer attention. However, his contribution was not particularly helpful as he indicated that he had recognised only 6 cases

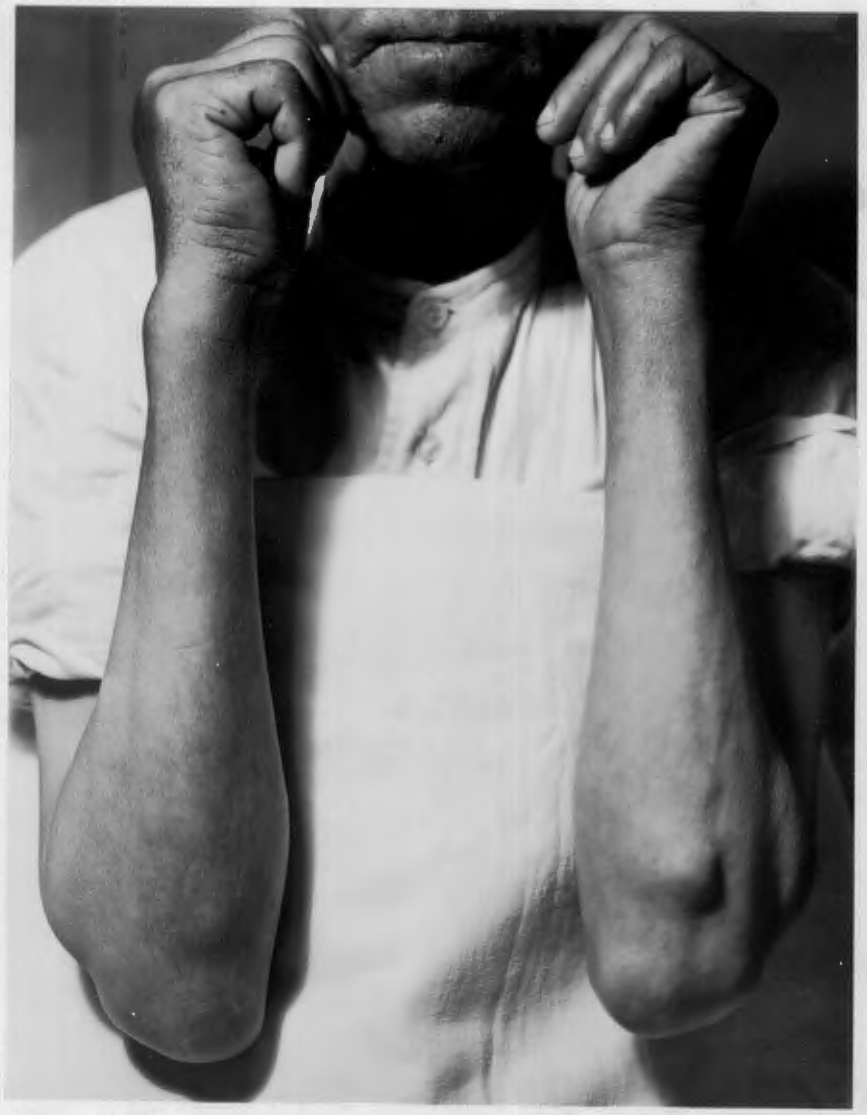
over...../

over a period of 8 years. If he has only been able to collect 6 such examples in the numerous cases of tuberculosis in children which he probably has seen, then his conclusions do not suggest that there is any special justification for the term "Tuberculous Rheumatism" as the occurrence of the arthritis may have been an example of a coincidental disease.

The occurrence of 2 cases of pulmonary tuberculosis in the series of 70 cases of rheumatoid arthritis is too low to draw any conclusions. Radiological evidence of pulmonary tuberculosis is not rarely encountered as an incidental finding in out-patients suffering from various maladies.

FIG. 28.

Subcutaneous Nodules.



Case 9 : Rheumatoid Arthritis.

Characteristic site of nodules along ulnar border 2" distal to tip of olecranon process.
Proved case of pulmonary tuberculosis.

Q. COMPARISON OF CLINICAL FEATURES IN EUROPEANS AND NON-EUROPEANS.

There were no obvious dissimilarities noted between the clinical features in the European cases and in the Non-European cases. This is in keeping with the common finding that there is no essential difference between the clinical features of the major medical infective and non-infective diseases in the European and in the Cape Coloured population of Cape Town.

S E C T I O N 111.

- THE SUBCUTANEOUS NODULES OF RHEUMATOID ARTHRITIS.

A. CLINICAL FEATURES.

1. REVIEW OF THE LITERATURE.

KEIL (1938) reviewed many aspects of the subcutaneous nodules of rheumatoid arthritis very thoroughly and extensively. His article included numerous references to the older observations and contributions to the literature.

The clinical features of the nodules have been described by several workers, viz. DAWSON and BOOTS (1930), DAWSON, SIA and BOOTS (1930), CLAWSON and WETHERBY (1932), WETHERBY (1932), DAWSON (1933), COLLINS (1937, 1939), BENNETT, ZELLER and BAUER (1940), WEBER (1944, 1947), FLETCHER (1946, 1947), KERSLEY, GIBSON and DESMARAIS (1946), LUCCHESI and LUCCHESI (1947) and by RAVEN, WEBER and PRICE (1948).

(a) Incidence.

The reported incidence of the occurrence of subcutaneous nodules in rheumatoid arthritis has varied considerably in different series. The Committee of the American Rheumatism Association ("Primer on Arthritis", 1942) stated that the nodules "occur in 15 to 20 per cent of cases". COMROE (1944), after having reviewed the literature, noted that the nodules may appear in 5 - 25 per cent of cases of rheumatoid arthritis. He observed that the percentage "undoubtedly varied tremendously in

various ...../

various areas", and stated that in Philadelphia they do not see these nodules in more than 5 per cent of cases, even though they are searched for most diligently. The incidence of nodules in this local series of cases will be discussed below.

DAWSON and BOOTS (1930) found subcutaneous nodules in 40 out of 200 patients with rheumatoid arthritis - an incidence of 20 per cent. They suggested that the incidence "among patients at large" was possibly somewhat less as their attention was focussed "on this particular phenomenon".

CLAWSON and WETHERBY (1932) found subcutaneous nodules in 59 out of their 200 patients with "chronic arthritis" - an incidence of 29.5 per cent - but their conclusions are of no value as, according to their own statements, their series included cases of osteoarthritis. In the same year WETHERBY (1932) published his findings in 350 cases of "chronic arthritis"; subcutaneous nodules were present in 94 cases - an incidence of 31.5 per cent. This latter series presumably included his earlier 200 patients. The same criticism may be made again as cases of osteoarthritis with Heberden's nodes were included in the series. Observers who have published reports on the subcutaneous nodules after the appearance of WETHERBY's papers, e.g. DAWSON (1933) and COLLINS (1937), mentioned his conclusions, and his findings

have...../

have thus been perpetuated in the literature. COLLINS (1937), e.g. quoted the "high incidence" of subcutaneous nodules detected by Wetherby in patients with "rheumatoid arthritis", whereas Wetherby was reviewing a miscellaneous series of cases of "chronic arthritis"!

DAWSON (1933) reported the occurrence of 66 cases with nodules in a series of 245 patients with rheumatoid arthritis - an incidence of 25 per cent, whereas COLLINS (1937) detected nodules in only about 7 per cent of patients with rheumatoid arthritis. LUCCHESI and LUCCHESI (1947 found 55 cases with subcutaneous nodules in a series of 290 cases of rheumatoid arthritis.

(b) Situation.

DAWSON and BOOTS (1930) found that the nodules occurred most commonly on the elbows, "at a point about 4 cm. distal to the olecranon". This special "site of predeliction" has been noted by other investigators. They also noted their occurrence over the olecranon process itself; in the wall of the olecranon bursa; over the dorsum of the forearms and hands; and over the knees, sacrum and scalp. DAWSON (1933) quoted a series of 66 cases with subcutaneous nodules and stated that nodules occurred over the "elbows" in 60 instances. Nodules occurred less

commonly ...../

commonly on the knees, ankles, occiput (in 2 instances only), knuckles and sacral spine. He noted that the nodules sometimes occurred in several locations in the same patient and that they were not infrequently symmetrical and bilateral. The symmetrical distribution has also been noted by other observers. COLLINS (1937) found that the nodules usually occurred over bony prominences, mainly in the neighbourhood of joints. He also observed that "the subcutaneous border of the ulna, within 1" or 2" distance of the olecranon, was much the commonest site". Nodules were sometimes found, too, in "other sites where bone approaches skin", e.g. knuckles, scalp, vertebral spines, patellae and tibial malleoli. In his experience multiple nodules occurred as frequently as single ones. In some cases the nodules are extremely numerous (NELIGAN, 1935). FLETCHER (1947), on the other hand, considered that the nodules were seldom multiple.

BENNET, ZELLER and BAUER (1940) stated that the subcutaneous nodules were usually multiple. In a series of 44 cases with nodules they were multiple in 36 instances. The vast majority of the nodules occurred at the "elbow" but they do not indicate whether they were situated over the olecranon process or distal to it. It was not possible to determine the exact distribution of the nodules as they did not include full data in their article.

WEBER...../

WEBER (1944) reported a few cases of rheumatoid arthritis with subcutaneous nodules; enlarged synovial bursae with thickened walls; ganglia; and juxta - articular thickenings of tendon insertions and tendon sheaths. In the discussion on these cases he observed that the distribution of nodules along the ridge of the ulna of both forearms, from elbow to wrist, was "very characteristic". FLETCHER (1947) published a photograph of a nodule in the tendo Achilles and stated that this was a fairly common finding in rheumatoid arthritis.

LUCCHESI and LUCCHESI (1947) analysed the distribution of a total of 289 nodules in 55 patients. They found that 70.5 per cent were situated on the upper limbs, 17.6 per cent on the "trunk", 10.7 per cent on the lower limbs and only 1.1 per cent on the head. It would have been a source of great interest if they had stated a detailed analysis of the site affected in the upper limbs as this is one of the largest series described. It is interesting to note how rarely the head was affected in contrast with the frequent occurrence of subcutaneous nodules on the occipital region in cases of rheumatic fever.

COMROE (1944) mentioned the findings of various observers and stated that the nodules were most commonly

found...../

found on the dorsal surface of the forearm, 1" - 2" below the elbow joint, confirming the opinion expressed by other authors.

RAVEN, WEBER and PRICE (1948) have very recently described a most interesting case of rheumatoid arthritis with subcutaneous nodules in which, at post mortem, numerous macroscopic nodules were visible in the pericardium, endocardium, lungs, pleurae and larynx. Photographs are published indicating their findings. The histological appearances of the cardiac nodules resembled those seen in the subcutaneous nodules. WEBER (1948) was sufficiently impressed by this case to state that he was "personally in favour of classifying rheumatoid arthritis among the infectious granulomata".

(c) Size.

The size may vary from small, scarcely palpable, seedlike bodies to large excrescences, the size of olives (DAWSON and BOOTS, 1930). They usually vary between 1 & 2 cm. in diameter. FLETCHER (1947) noted that the size depended to some extent on the duration and age of the patient. Nodules situated over the olecranon process, or in the olecranon bursa, may form a bulky nodular swelling and reach the size of one or 2 walnuts.

(d)...../

(d) Consistency.

They may be soft, moderately firm or quite hard. Consistency tends to vary directly with the duration of the nodule.

(e) P a i n.

Most observers stress the absence of pain and tenderness but KEIL (1938) stated that these features may sometimes be present.

(f) Relationships.

They are characteristically situated in the subcutaneous tissue and are not adherent to the skin. DAWSON and BOOTS (1930) stated that they are not attached to underlying periosteum, but most authors indicate that they are sometimes attached to the periosteum. They are not infrequently attached to tendon sheaths and to bursal walls as has been mentioned above. Occasionally the skin is ulcerated over the nodule as a result of repeated trauma.

(g) Duration.

DAWSON (1933) stated that the nodules usually persist for months or years in the majority of cases, but that smaller ones may disappear in the course of a few weeks.

(h) ...../

(h) Significance and Prognosis.

Several observers have associated the presence of subcutaneous nodules with a bad prognosis. DAWSON (1933) e.g. was emphatic that the "presence of nodules in rheumatoid arthritis almost without exception indicates a severe form of the disease and, as a rule, their persistence is associated with a bad prognosis." COMROE (1944) also maintained that the presence of such nodules was often an indication of a poor prognosis. The Committee of the American Rheumatism Association ("Primer on Arthritis", 1942) considered that subcutaneous nodules were more fequently observed in severe cases and that the prognosis of the disease was unfavourable if subcutaneous nodules developed.

LUCCHESI and LUCCHESI (1947) undertook an investigation to determine whether this widely accepted view was correct or not. They studied 55 patients with rheumatoid arthritis who had subcutaneous nodules. They found no evidence that a "graver or more intense form of rheumatoid arthritis" was present in these cases with nodules. They commented particularly on 3 cases of rheumatoid arthritis of 23, 30 and 50 years duration respectively, which were in "good health" and which were able "to get about quite well in spite of extensive ankylosis".

An interesting point emerged from their

investigations...../

investigations. They noted the development of nodules in some cases of rheumatoid arthritis which were in their terminal stages with normal sedimentation rates. In one case the nodules appeared in the 49th. year of the illness, i.e. at the "terminal stage", without subjective or objective manifestations or any deterioration in general condition or in that of the joints. (They apparently use the expression "terminal stage" to designate the stage of painless ankylosis, deformities and contractures which others refer to as the "burnt-out" stage). In another case with a normal sedimentation rate nodules appeared after the patient had been gaining weight and improving for the past 15 months. He was subsequently discharged in excellent general condition with "practically normal joints". They concluded that, in contradistinction to the findings in rheumatic fever, the appearance of subcutaneous nodules in rheumatoid arthritis did not indicate activity or exacerbation of the disease. It must be conceded that they have quoted definite examples in which the appearance of nodules occurred in quiescent or in improving cases.

They also attempted to compare the results of "treatment" (the details of which were not stated) in the cases of arthritis with and without nodules. Their 55 cases consisted of 15 in the "terminal stage"

and 40 ...../

and 40 "advanced" cases. They claimed that the "treatment was satisfactory" in these cases of rheumatoid arthritis with nodules and "in no way inferior" to the results achieved in patients with rheumatoid arthritis without nodules! One presumes that their definition of "satisfactory treatment" means no more than "some improvement" after physiotherapy, etc. as they were handling a group of cases in whom "cures" or "great improvement" seemed impossible.

KEIL (1938) suspended judgement on the relation of the nodules to the eventual outcome. He noted that there are many cases exhibiting nodules for protracted periods, occasionally even decades, and that, on the other hand, patients with the most crippling forms of the disease may be free from nodules.

2. RESULTS OF PRESENT INVESTIGATION.

Incidence of Subcutaneous Nodules.

Of the 70 cases examined 20 had either one nodule or multiple nodules. The incidence of nodules in the cases was therefore approximately 29 per cent.

Number and Distribution of Nodules.

Eight of the 20 cases had one nodule, and 12 cases had 2 or more nodules. A total of 99 nodules were found in these 20 cases. Table 6 illustrates the total number of nodules found in each case; and Table 7 illustrates the distribution of these nodules in the various situations.

TABLE 5. NUMBER OF NODULES IN EACH OF 20 CASES.

Case	Total Number of Nodules	Age (years)	Duration of Arthritis (years)	Duration of Nodules (years)	Photographs (Figures)
2	1	43	6	?	81
4	1	47	1	?	
6	4	78	43	11-12	53
7	2	51	3	3/12	
9	4	53	2	1½	28
10	1	51	5	1½	
17	2	49	3½	5 weeks	
18	1	35	8½	3	
19	13	55	35	±30	
25	1	60	1	9/12	29
26	18	53	45	±15	67
30	1	48	2	?	
35	1	44	11	9/12	39
39	14	35	10	±8	30
46	16	72	30	many years	
56	1	70	4	3	49
58	5	66	8	±6	32
62	3	52	8	1	
67	8	77	11	?	33
69	2	60	7	3	38

TABLE I. DISTRIBUTION OF NODULES IN 20 CASES

Case	Total Number of Nodules	Fingers	Dorsum of Wrists	Ulnar Border 1-2" Distal to Olecranon Tip	Olecranon Process	Ear	Extensor Tendons of Toes	Patellae	Tendo Achillis	Ankles and Feet	Sacrum
2	1			1(L)							
4	1				1(L)						
6	4			1(L)	1(L) 2(R)						
7	2			1(L)	1(R)						
9	4			2	2						
10	1										1
17	2			2							
18	1				1(L)						
19	13	5(R) 2(L)			2		2		2		
25	1			1(R)							
26	18	5(R) 4(L)		2	2		2		2	1	
30	1				1(R)						
35	1					1(R)					
39	14	3(R) 1(L)		2	2				3(R) 2(L)	1	
46	16	4(R) 3(L)		2(R)	4		2		1(R)		
56	1			1(L)							
58	5				3(R) 2(L)						
62	3				3(L)						
67	8	3(R) 3(L)	1(L)		1(L)						
69	2							2			
Total: 99		33	1	15	28	1	6	2	10	2	1

FOOTNOTE: R - right
L - left

If R and L are not inserted it indicates that the nodules were present bilaterally.

3. D I S C U S S I O N.

There is a high incidence of subcutaneous nodules in this series, viz. 29 per cent. This is approximately the same incidence (25 per cent) which was recorded by DAWSON (1933).

12 of the 20 cases had nodules in one or more situation. The presence of more than 5 nodules per case was noted in 5 cases which had 13, 18, 14, 16 and 8 nodules each respectively. This finding indicates how numerous and widespread the nodules may be in certain cases.

The distribution of the total of 99 nodules was analysed and the ulnar border of the forearm was found to be a very common situation (15 nodules). Thirty-three nodules occurred on the fingers but this total includes the numbers present on any of the 5 digits. The olecranon process of the elbow was actually the commonest site at which the nodules occurred (28).

DAWSON found the "elbows" to be the commonest

site ...../

site at which the nodules occurred in his series, but he has included both the olecranon process and the ulnar border under the common heading of "elbows". Other observers have also not differentiated between these 2 sites. If we also group these 2 sites together then it will be seen that 43 nodules occurred at the "elbows". This confirms the reported frequency with which nodules occur at the "elbows".

An interesting feature noted was the quite common occurrence of nodules in the Achilles tendon (Fig. 77) and in the extensor tendons of the toes (Fig. 79). The nodules in the extensor tendons of the toes occurred about 3½" proximal to the anklejoint in the anterior compartment of the leg (Fig. 79).

The nodules on the fingers nearly always occurred on the dorsal surface, often over a metacarpophalangeal or an interphalangeal joint. (Fig. 75). In one case (Case 38) the nodules were situated on the palmar aspect of the thumbs (Fig. 31). In one case (Case 69) the nodules occurred on the

summit ...../

summit of the patellae (Fig. 38). In Case 35 a nodule was found on the most lateral point on the pinna of the right ear (Fig. 39). It had the characteristic histological appearances of the necrobiotic nodules of rheumatoid arthritis (Fig. 42).

The features of the nodules conformed on the whole with the standard descriptions as regards size, shape, consistency, surface and relationship. None of the nodules were painful or tender. They were not adherent to the skin with the exception of the nodules at the summits of the patellae in case 69 (Fig. 38). Some were slightly or even firmly adherent to underlying periosteum while others were well-defined. They all had limited ranges of movement in the subcutaneous tissue with the exception of a very hard nodule over the left elbow in Case 57 which had a wide range of mobility (Fig. 49). The sizes varied widely. A few tiny nodules were encountered, 3-5 mm. in diameter, and all grades occurred up to large lobulated nodules, twice the size of walnuts, situated over the olecranon processes..

Some of the smaller nodules present over the olecranon processes were obviously within the olecranon bursa or were attached to its lining; and thickened bursal tissue or fluid could be detected around these particular nodules (Fig. 32). Two interesting features were commonly observed in the nodules which occurred

over...../

over the olecranon process. Firstly, they were very often lobulated and often consisted of 2 or 3 tiny nodules closely linked to each other to form a small or moderate-sized nodule. Secondly, in the old-standing cases, the largest nodules in each instance were present at this site - and were also strikingly lobulated and nodular (Figs. 36 and 72). These special features are probably due to the origin of these olecranon nodules from the olecranon bursa itself. The duration of the nodules varied from 3 months to approximately 30 years. The older nodules were usually larger than the earlier ones but several exceptions occurred, e.g. in Case 6 they were bean-sized although their duration was longer than 11 years. Table indicated that the nodules developed a variable interval after the onset of the arthritis.

The nodules usually had the colour of the overlying skin. Others were slightly reddish and some were slightly pale. Several nodules, chiefly the large ones situated over the olecranon processes, had a slightly yellowish colour and might erroneously be diagnosed as xanthomata.

In the vast majority of cases there was no development of new nodules or disappearance of old nodules during the year in which they were under observation. A few exceptions occurred. Case 7 had

nodules...../

nodules over each elbow on admission which had been present for 3 months. One was removed by biopsy and the other had practically disappeared spontaneously a year later. Case 66 had multiple nodules on the hands (Fig. 16) and one nodule near the left elbow which was removed by biopsy. A "recurrence" of the nodule was noted at exactly the same site several months later (Fig. 33).

Other cases mentioned in their past history that nodules had appeared and then disappeared. Case 35 had nodules near both elbows 4 years ago which disappeared 2 years ago and she had no further nodules until one developed on her right ear 9 months ago. 2 further cases in the series of 50 cases which had no nodules on examination gave a past history of the temporary occurrence of nodules on the elbows and on the occiput (Cases 49 and 53 respectively). These nodules persisted for several months before they disappeared.

All these features noted in the past histories and during the present year of observation confirm the fact that the smaller nodules of rheumatoid arthritis may regress and disappear like the nodules of rheumatic fever.

FIG. 29.

Subcutaneous Nodules.

Case 25: Rheumatoid Arthritis.

Nodule on right forearm, 1½" distal to tip of olecranon process.

FIG. 30.

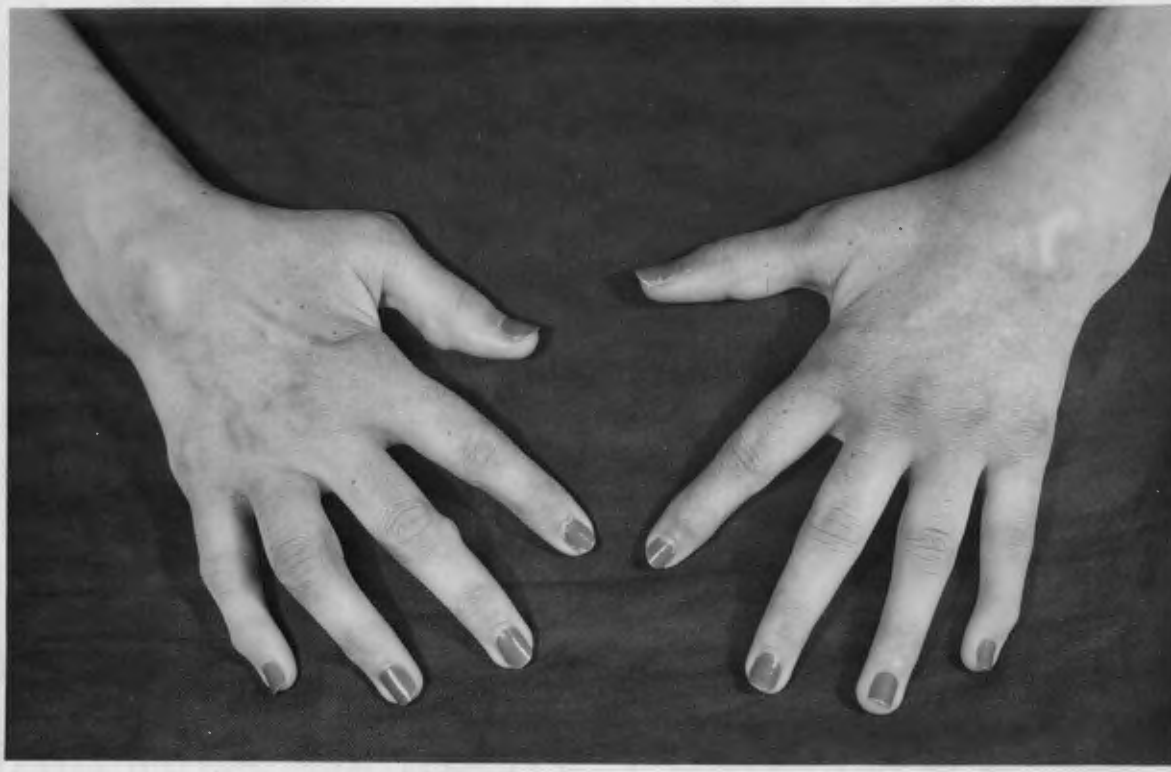
Subcutaneous Nodules.

Case 39 : Rheumatoid Arthritis.

Large nodules situated over the olecranon process and along the ulnar borders, 2" - 3" distal to the tip of the olecranon process.

FIG. 31.

Subcutaneous Nodules.

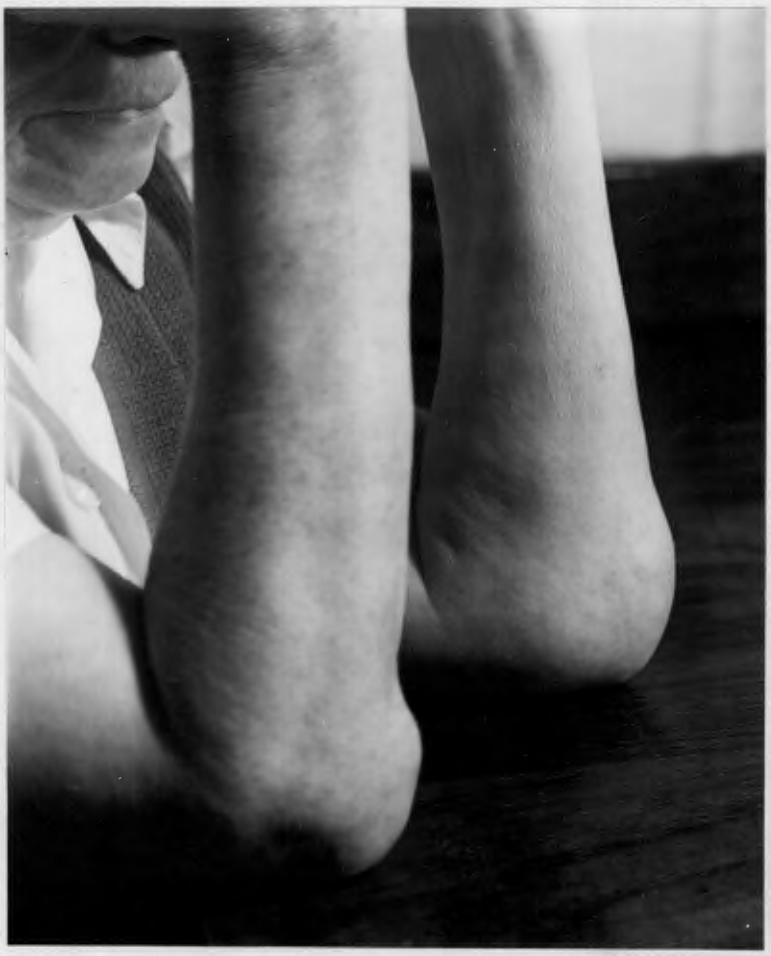


Case 39 : Rheumatoid Arthritis.

Nodules situated on fingers and on palmar aspects of thumbs.
"Carpal Cysts" over dorsum of wrists.
(See Fig. 30).

FIG. 32.

Subcutaneous Nodules.

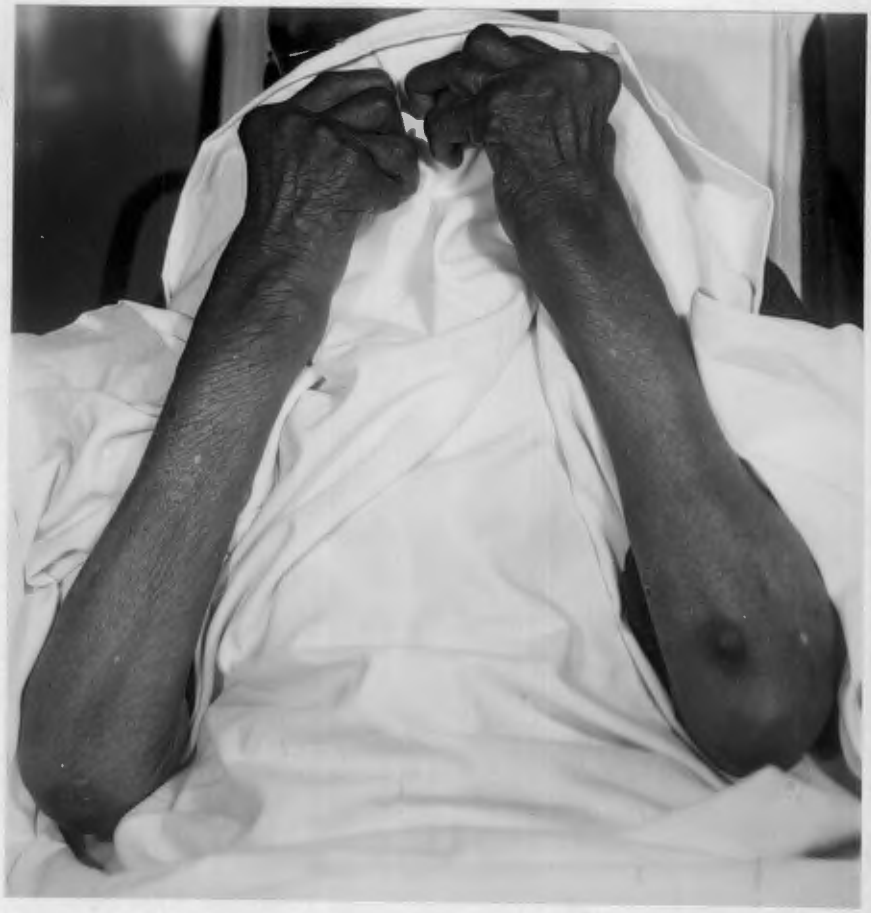


Case 58 : Rheumatoid Arthritis.

Several nodules in each thickened olecranon bursa.

FIG. 33.

Subcutaneous Nodules.



Case 66 : Rheumatoid Arthritis.

"Recurrence" of nodule on left forearm after previous removal.
(See Figs. 16 and 17 for appearances of hands).

4. The Role of Trauma in the Production of the Nodules.

(a) Experimental Production of the Nodules.

MASSELL, MOTE and JONES (1937) were impressed with the possibility that trauma might be a factor in the production of the subcutaneous nodules in rheumatic fever. They therefore traumatized the elbows of "rheumatic fever subjects" by several methods to see if the nodules could be artificially induced.

They investigated 116 patients. The series included (i) 60 cases with rheumatic fever (of whom 20 had clinical manifestations, 26 had only laboratory evidence of infection and 14 were convalescent without clinical or laboratory evidence of active disease);

(ii) 22 cases with chorea.

(iii) 34 control cases (with diseases other than rheumatic fever, e.g. bone tuberculosis).

The region of the olecranon process was infiltrated with 1 per cent novocaine in each of the 116 patients. 2-3 cc. blood were removed from the antecubital vein and immediately injected into the subcutaneous tissues of the anaesthetised area. The patients rubbed the injected elbows on the bedclothes for several minutes 6 times daily for the next 10 days.

Of the ...../

Of the 20 cases with clinical rheumatic fever, 18 developed nodules.

Of the 26 cases with laboratory evidence of rheumatic fever, 13 developed nodules.

Of the 14 cases without clinical or laboratory evicence of active infection, only 2 developed nodules.

Of the 22 cases of chorea, 3 developed nodules.

Of the 34 controls, only one case developed a nodule.

This experiment appears to indicate that cases of rheumatic fever have a much greater tendency to develop subcutaneous nodules due to trauma than non-rheumatic cases. The results also indicate that the nodules develop more readily when the disease was active than when it was inactive.

These workers also performed control experiments which showed that novocaine injection followed by trauma (without the injection of blood) did not lead to the development of nodules. On the other hand, some cases developed nodules if blood was injected even if no friction was applied afterwards; and similarly some cases developed nodules after the injection of saline, even if no friction was applied afterwards.

In another publication (MASSELL, MOTE and JONES, 1937), the authors examined these induced nodules histologically and considered that they bore a great

resemblance.....

resemblance to the spontaneously occurring nodules in rheumatic fever.

MASSELL, MOTT and JONES (1937) consider that they have proved the importance of trauma in the production of the subcutaneous nodules in cases of rheumatic fever. However it seems that nodules sometimes appeared after the injection of blood or saline even if not followed by trauma! The authors suggested that the introduction of the blood might constitute the trauma in these latter cases. They also suggested that the introduction of 2 - 3 cc. saline is probably attended by some bleeding which would then act as the "trauma". Even if these suggestions were accepted it would mean that the term "trauma" had become very much widened in its concept practically equivalent to "tissue injury" in a very broad sense. These observers have thus not succeeded in proving the importance of external trauma as a factor in the development of the subcutaneous nodules of rheumatic fever.

HART (1939) noted the work of the above workers and attempted to reproduce it. His series included cases of rheumatic fever, cases of "Still's Disease" and control cases suffering from non-rheumatic conditions. He followed the technique outlined by the above workers, but the results were entirely negative - none of the cases developed nodules at the site of trauma. In 2 cases where blood was

injected...../

injected over the internal malleolus, "Nature provided fresh nodules within a week over the external malleolus", but none appeared over the experimental area! That is, nodules appeared spontaneously but attempts to produce them experimentally failed completely.

As Hart's cases were children it might be thought that they perhaps neglected to exert friction over the injected areas and that this was the explanation of his inability to confirm the earlier work. HART admits that "it is unlikely that only a few minutes daily were spent in rubbing" in many cases, but stated that no "different results were obtained in 12 cases who were known to persevere with their exercises and were seen constantly throughout the day."

(b) Clinical Evidence and Discussion.

COLLINS (1937) noted that the sites at which the subcutaneous nodules of rheumatoid arthritis occurred were areas exposed to pressure or trauma and considered that mechanical injury might play a part in determining their occurrence, location and chronicity. WEBER (1944) and KERSLEY, GIBSON and DESMARAIS (1946) described the occurrence of nodules, for example, over the acromial process of the scapula. COLLINS (1937) noted that the presence of large nodules over the ulnar were almost invariably associated with arthritis of the wrists so that the ulna became the weight bearing part in such actions as rising from a chair.

While the cases were being interrogated and examined attention was paid to the possible role of trauma in the production in and the localisation of the nodules. A considerable amount of interesting information was obtained and is briefly summarized below.

Firstly, the sites at which the nodules occurred most frequently (viz. olecranon processes, ulnar border and fingers) were the areas which are most often subjected to trauma in rheumatoid arthritis. The patients often learn how to elevate themselves in bed by pressing the elbows against the bedclothes and may manage to arise from a chair by using the ulnar border of the forearm as the lever. It is interesting..

to note...../

to note that if one is sitting on a chair at a table and then attempts to rise without the use of the hands, then the site used for leverage is usually the ulnar border of the forearm, approximately 2 inches distal to the tip of the olecranon - one of the common sites at which nodules occur in the disease.

Case 1 was bedridden with bony ankylosis of the hands and wrists (Fig. 81). His legs had been amputated above the knees and the hips were completely ankylosed. He could only manage to move in bed by pressing against the bedclothes with his elbows, and he had a nodule on the left ulnar border. (Fig. 82)

Case 7 had rheumatoid arthritis for 3 years during which time he was bedridden. After being admitted to the Conradie Home he was given a self-propelled wheelchair. In getting from the wheelchair to the bed he used to press his elbows on the arm rests of the wheelchair and nodules developed on both elbows within a few weeks. After the nodules were present for three months he was admitted to hospital for a series of orthopedic manipulations to his knees. He used to be lifted by assistants in and out of his bed and wheelchair and one nodule decreased in size and is just detectable. This marked reduction in size might be the natural history of this nodule but trauma seemed to be a very important factor in its production.

Case 10 ...../

Case 10 was one of the few completely bedridden cases in the series. She lay on her back all day and rarely moved her position; a nodule was present over the sacrum.

Case 17 had rheumatoid arthritis affecting the hands and wrists for 3 years and no nodules developed. 5 weeks before her admission the knees became acutely involved and were very painful and stiff. She found that the pain was less unbearable if she kept her knees flexed. However, with semi-flexed knees, she could no longer comfortably do the washing in her rather high kitchen sink - unless she propped her elbows on the edge of the sink. Nodules appeared at the characteristic site on the ulnar border (Fig. 34). It might be argued that the simultaneous occurrence of the arthritis of the knees and the subcutaneous nodules on the forearm was in each case merely an example of "activity" of the disease. However, the suggestion that a traumatic factor precipitated the appearance of the nodules seems reasonable.

Cases 19, 26, 46 and 67 had marked deformities of the hands (Figs. 75 , 9 and 16). Multiple nodules were present on the fingers over the knuckles. However, owing to the extensive deformities the normal anatomical positions of the metacarpophalangeal and interphalangeal joints had been altered, and the "new" knuckles were in different positions as compared with

their original sites. It is interesting to note that the nodules developed over the sites of the "new knuckles" i.e. at the summits of the points of greatest convexity! This again indicates the importance of the traumatic factor. Case 19 (not illustrated) stated in her history that the fingers gradually became deformed over a period of 10-15 years. Nodules developed one by one, on the respective knuckles a few years after they became deformed.

Case 69 had the grossest degree of flexion contracture of the knees which was noted in the series. She lay in bed constantly with her knees sharply flexed. No protective "bed-cradle" was used over the knees. Nodules developed at the highest points on the surface of each patella where it was pressed upon by the weight of the blankets (Fig. 38).

Case 35 developed a nodule on her right ear 9 months before her admission (Fig. 39). As the joints on the left side of the body were more painful than those on the right side she took to lying constantly on her right side. A nodule developed on the crus of the antihelix of the right ear (Fig. 39). This same patient had transitory nodules on her elbows 4 years ago which she attributed to her custom of using her elbows for levers on rising as her hands were too deformed. (Figs. 20 and 21). These elbow nodules persisted until she became bedridden on account of the

progression...../

progression of the disease 2 years ago. She no longer had to use her elbows as the nurses assisted her to sit up - and the nodules disappeared a few months later.

Case 25 volunteered her opinion that the nodule on her right ulnar border was due to pressure against the table as she rose from her chair (Fig. 29).

It is accepted, of course, that the presence of the underlying rheumatoid arthritis constitutes a liability to the development of nodules, and the results of the sedimentation rates showed that many seemingly "burnt-out" cases were still active. However, the conclusion thus appears to be that traumatic factors do play a large part clinically in the production and localisation of the subcutaneous nodules of the disease.

.. ..

FIG. 34.

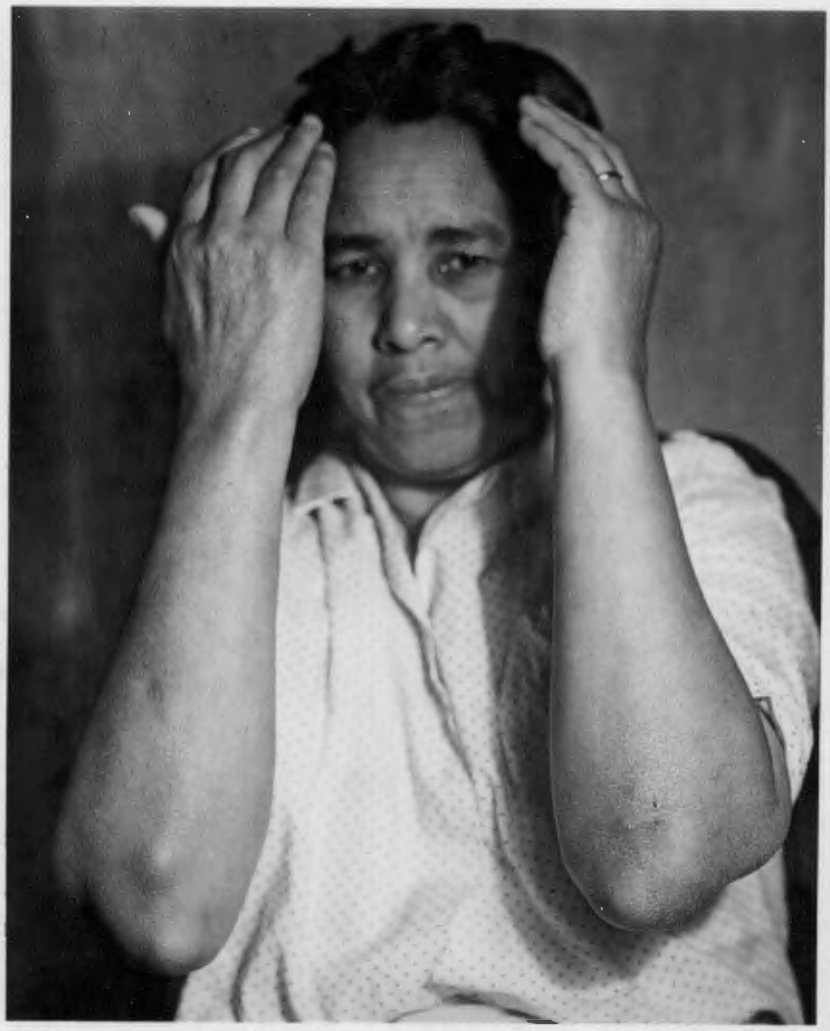
Subcutaneous Nodules.

Case 17 : Rheumatoid Arthritis.

Characteristic situation of nodules along ulnar border, 2" distal to tip of olecranon process. (See Fig. 35.).

FIG. 35.

Subcutaneous Nodules.

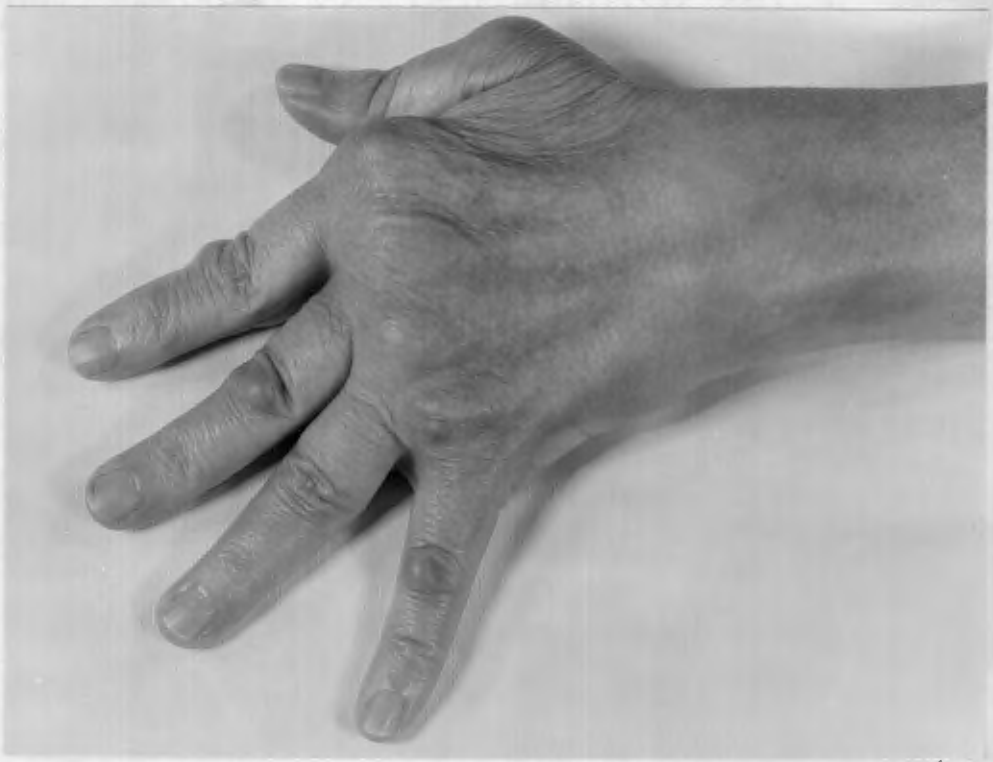


Case 17 : Rheumatoid Arthritis.

Photograph taken after biopsy of nodule on left forearm (See Figs. 34).

FIG. 36.

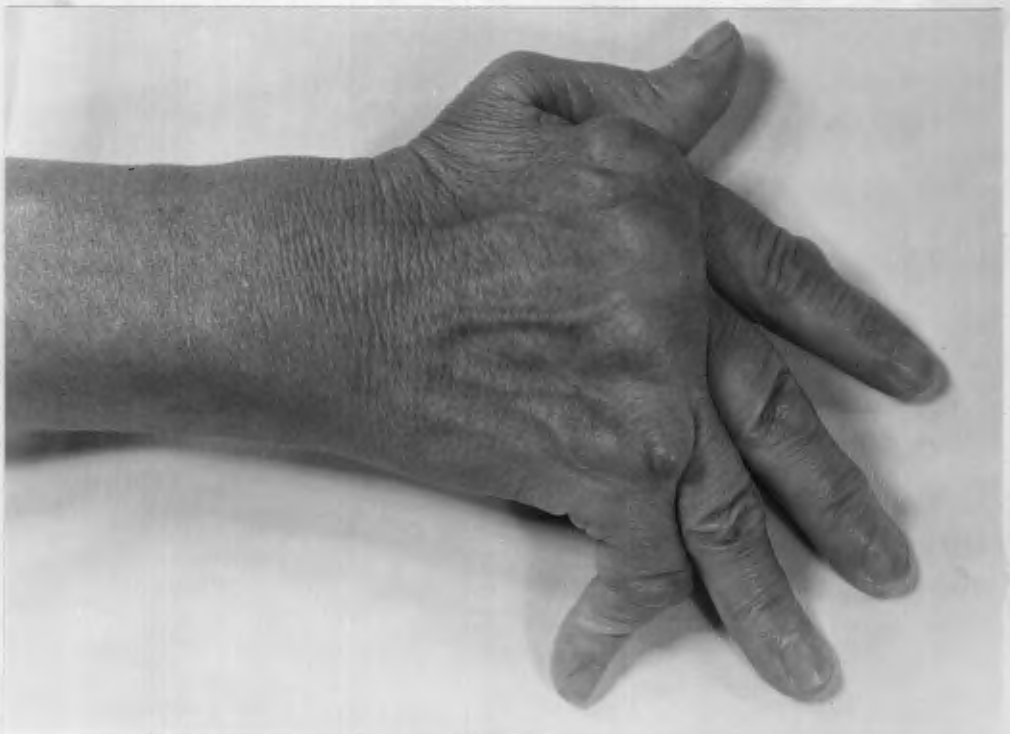
Trauma and Subcutaneous Nodules.



Case 26: Rheumatoid Arthritis.
Left Hand:
Numerous small nodules on dorsum of fingers situated over sites liable to be traumatised.
(see Fig. 37).

FIG. 37.

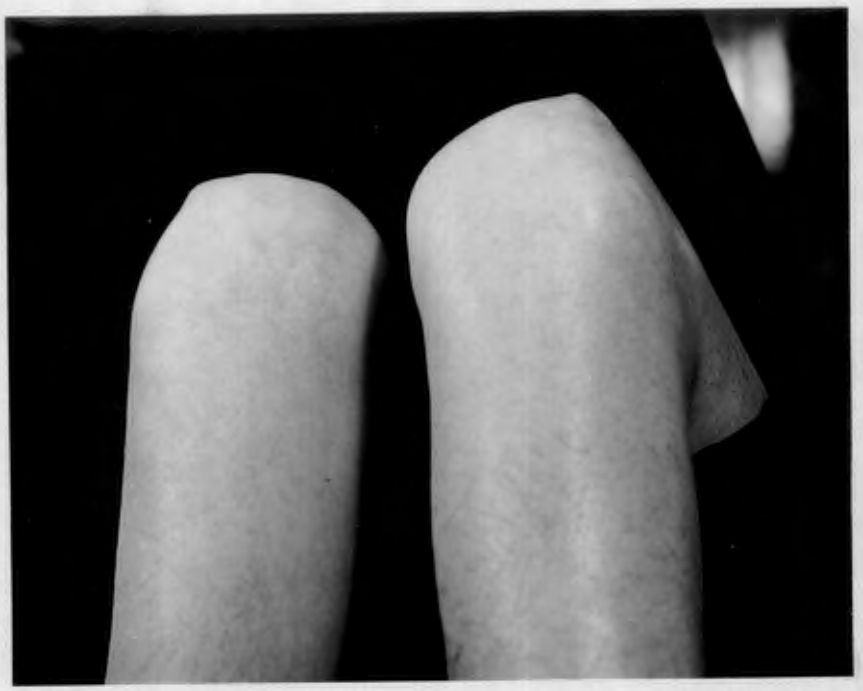
Trauma and Subcutaneous Nodules.



Case 26 : Rheumatoid Arthritis.
Right Hand:
Numerous small nodules on dorsum of fingers, situated over site liable to be traumatised.
2 tiny nodules on summit of flexed deformed proximal interphalangeal joint of little finger. (See Fig. 36).

FIG. 38.

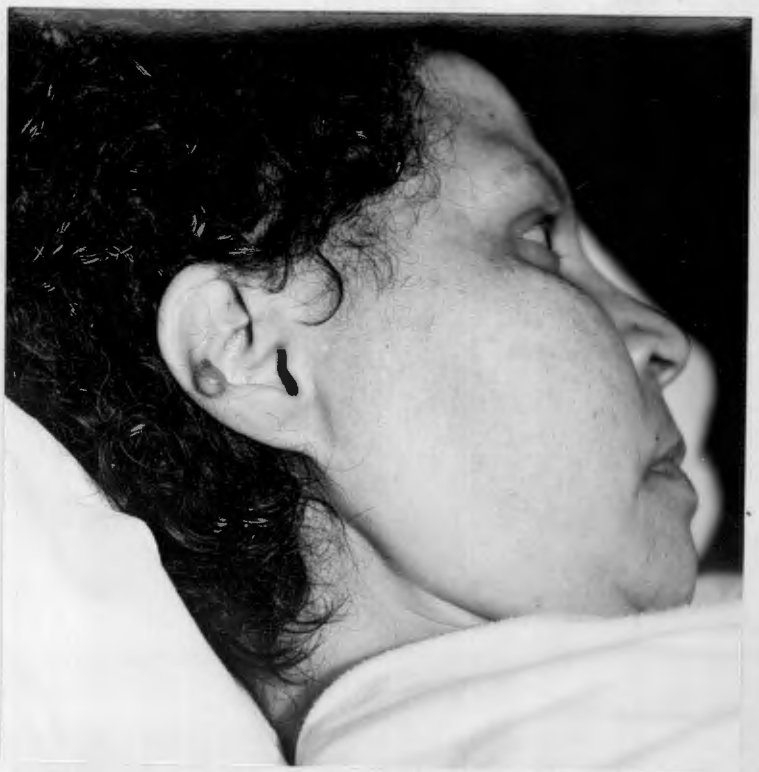
Trauma and Subcutaneous Nodules.



Case 69: Rheumatoid Arthritis.
Small nodules over patellae at sites of maximal convexity.
Gross contractive deformity of both knees.

FIG. 39.

Trauma and Subcutaneous Nodules.



Case 35 : Rheumatoid Arthritis.

Reddish subcutaneous nodule on pinna of right ear with characteristic histological appearances (See Fig. 42).
Patient lay on her right side since onset of arthritis.

5. SIGNIFICANCE OF SUBCUTANEOUS NODULES.

When the literature on the clinical features of the nodules was reviewed, the bad prognostic significance alleged to be attached to the presence of the nodules was mentioned.

Of the 20 cases with nodules 8 were inmates of the Conradie Home "for the Chronic Sick" and thus represented examples of the more advanced and deformed cases. It does seem, therefore, that there is probably a higher incidence of nodules present in the advanced deformed cases found in such institutions.

However the problem is whether or not the presence of these nodules indicates a bad prognosis. Admittedly the more deformed crippled cases in this series had a higher incidence of nodules than the younger earlier cases - but this does not prove that the presence of the nodules necessarily indicated a bad prognosis. The explanation might well be that it is these advanced deformed cases which are liable to develop nodules! The ultimate state of affairs would be the same - there would be a higher incidence of nodules found in association with the severer deformed cases, but the nodules may be the result, not the indicator, of a bad prognosis. If an observer maintains that the appearance of nodules indicates a bad prognosis (as does, for example, the appearance of pulsus alternans in a case of hypertension), then the onus

rests...../

rests on him to prove that early cases with nodules have a worse prognosis than early cases without nodules.

It is interesting to note that the 5 cases which had very many nodules (viz. Case 19 with 13 nodules, Case 26 with 18 nodules, Case 39 with 14 nodules, Case 46 with 16 nodules and Case 67 with 8 nodules) all had 2 features in common: firstly, they had gross deformity of the hands and of many other joints and were examples of late advanced cases of the disease with ankylosis, contractures and deformities (Figs. 75 , 30 , 9 and 16). Secondly, pain was either absent or negligible and they all endeavoured to lead as active a life as was possible under the circumstances and did housework, sewing and other occupations in spite of the great deformities. They thus exposed the deformed parts to multiple trauma and this may be the explanation of the multiplicity and size of the nodules which were present in these cases. These 5 cases, in spite of the gross objective anatomical evidence of the ravages of the disease, were actually in a better condition than some cases in the series which had no nodules but which had a persistent painful polyarthritis for many years.

Other instructive points also emerged during the investigation of these cases, e.g. Case 18 had a nodule over her elbow associated with the mildest possible form

of ...../

of rheumatoid arthritis. The arthritis was present for 8 years and the nodule for 3 years. She is still a very mild case. Case 26 developed the nodules about 30 years after the onset of the rheumatoid arthritis (Fig. 75) - i.e. nodules appeared when the disease was already largely "burnt-out" and their appearance was not a sign nor an accompaniment of an exacerbation of the arthritis.

Finally one must recall the evidence adduced to show the role of trauma in the development of some of the nodules.

When all this evidence is added up, it appears that nodules can appear and disappear without any necessary exacerbation of arthritis; that nodules may never appear in severe progressive cases; that nodules may only appear when the arthritis is quiescent or "burnt-out"; that traumatic factors probably play a part in the production and localization of the nodules and that there is, as yet, no clear evidence that the presence of nodules indicates a bad prognosis. It is admitted, of course, that the incidence of nodules is highest in the more chronic deformed type of case but this may be merely the <u>result</u> of the severe deformity.

Thus the significance of the development of nodules in <u>early</u> cases (e.g. Case 17) remains to be solved; and the significance of the development of nodules in <u>oldstanding</u> cases with ankyloses and deformities is probably that they are the <u>result</u> of the arthritic havoc.

B. PATHOLOGICAL FEATURES.

1. REVIEW OF THE LITERATURE.

The histological appearances of the nodules have been fully described by DAWSON and BOOTS (1950); DAWSON (1950); COLLINS (1937, 1939); BENNETT, ZELLER and BAUER (1940); WEBER (1944); and KERSLEY, GIBSON and DESMARAIS (1946). CLAWSON and WETHERBY (1932) also described the histological appearance of nodules in their series of miscellaneous cases of "chronic Arthritis".

These workers agreed in their descriptions of the essential histological features of the nodules. Each nodule consists of single or multiple lesions of varying size. The characteristic lesions consist of the following structures:

(a) A central area of necrosis;

(b) An intermediate zone surrounding the necrotic centre and consisting of large, mononuclear cells which are mostly arranged in radial fashion, resembling a palisade. It is this radial arrangement which is chiefly responsible for the highly characteristic appearance of the whole lesion

(c) A peripheral zone consisting of corrective tissue which is usually dense and relatively avascular.

The area of central necrosis presents great

variation...

variation in different nodules. DAWSON (1933) considered that its appearance was in part determined by the size of the area involved and in part by the duration of the process. In smaller and earlier lesions there is a small and not well-defined area of focal necrosis which may show well-marked inflammatory cell infiltration. The necrotic areas are larger in older nodules. DAWSON (1933) noted that the necrotic material sometimes becomes liquefied In the centre of many of the larger nodules a process of cystic degeneration is sometimes apparent and amorphous clumps of necrotic tissue may lie free in the centre of large cystic cavities. DAWSON (1933) also made the interesting observation that the central necrotic material may undergo further alterations; it may lose its homogenous appearance and numerous large rhomboidal crystals of cholesterol may be deposited in it. COLLINS (1937) noted that the solid necrotic centre may become liquefied and be gradually dispersed; when this happens the surrounding connective tissue may condense into a smooth cellular lining resembling a simple type of bursal or synovial lining.

(B). In the intermediate cellular zone of mononuclear cells there may also be cells surrounding clumps of disintegrating material forming large foreign-body giant cells. A variable cellular infiltration, consisting

chiefly ...../

chiefly of lymphocytes and monocytes is sometimes present. In some sections there are considerable polymorphs and sometimes scattered eosinophils.

(c). The peripheral zone, unlike the central and intermediate zones, has not got a striking or distinctive appearance. There is often a variable degree of cell infiltration into the corrective tissue; the cells are chiefly lymphocytes but varying numbers of plasma cells, polymorphs and eosinophils may be present.

Vascular lesions have been described in the vessels in the peripheral zone and in the corrective tissue around the peripheral zone. The vascular changes consisted chiefly of perivascular infiltration of inflammatory cells, but BENNETT, ZELLER and BAUER (1940) noted that diffuse inflammation and degeneration of the entire wall of the bloodvessel were frequently present. Arterioles and capillaries may be affected. Thrombosis has been noted in some cases.

COLLINS (1937, 1939) considers that the earliest lesion is proliferation of new fibrous tissue and of less differentiated corrective tissue cells. His view is that a "fibrinoid degeneration" then commences in the avascular centre of this new tissue and spreads outwards; and that the radially arranged layer of cells represents

"a.....

"a rearguard action of cells in retreat from advancing necrosis, and not the vanguard of organisation". Other observers consider the necrosis to be primary and the cell reaction to be secondary.

KERSLEY, GIBSON and DESMARAIS (1946) reported on the histological appearances of 26 nodules removed by biopsy in various "rheumatic diseases". Their cases were mainly rheumatoid arthritis and gout. Many of their nodules in cases of rheumatoid arthritis had the characteristic histological features described by DAWSON (1933) and by COLLINS (1937), but some of the microscopical appearances warrant special attention. They described a nodule in a case of rheumatoid arthritis which consisted of an inner zone of very dense fibrous tissue with few nuclei and an appearance of scar tissue. The peripheral zone was vascular and the vessels were associated with "copious lymphocytic infiltration". The lymphocytes were chiefly paravascular in distribution and the appearances closely resembled those described in nerve and in muscle in rheumatoid arthritis.

Another of their cases showed numerous giant-cells in some fields at the margin of necrotic zones.

One nodule removed from the elbow of a patient with rheumatoid arthritis consisted of fibrous tissue and

fat. There was no necrosis, fibrinoid degeneration or evidence of characteristic cell reaction. A cleft ran through the middle of the nodule, lined in part by a flattened layer of fibrous tissue. They considered that it was a "traumatic nodule commencing to form an adventitious bursa". It is not easy to exclude the possibility, though, that this was a nodule which had arisen from the wall of the olecranon bursa.

(b) Results of Present Investigations.

Some nodules were easily removed, while others were adherent to underlying periosteum.

The 19 nodules were examined macroscopically after removal. They were round or oval in shape and varied in size from ½ - 2 cm. Some were well-defined while others were ill-defined and surrounded by varying amounts of subcutaneous tissue removed with the nodules at the biopsy. One nodule (Case 6; Fig. 56) was found to consist mainly of lipoid and cholesterol, and another nodule (Case 56; Fig. 50) had extensive calcification - these 2 nodules will be discussed in detail in later sections of this thesis. The main histological features of the other 17 nodules are summarized in Table 8.

TABLE 8.

RESULTS OF HISTOLOGICAL EXAMINATION OF 17 SUBCUTANEOUS NODULES

Case	Situation of Nodule	Duration of Nodule (years)	Diameter of Nodule (cm)	Histological Appearances.
2	Ulnar border	?	½	Cellular fibrous tissue without necrosis and without palisade formation. (Fig.47)
4	Olecranon process	?	½	Moderately vascular corrective tissue without any characteristic necrotic foci. One minute area of necrosis was present.
7	Ulnar border	3/12	1	A few foci consisting of central necrosis surrounded in parts by radially-arranged mononuclear cells. The nodule consisted mainly of cellular granulation tissue and of more collagenous fibrous tissue. Several areas of strandlike hyaline material were found, resembling "fibrinoid degeneration" and surrounded in part by moderate numbers of polymorphs.
9	Ulnar border (Fig.28)	1 - 2	1	Numerous characteristic foci consisting of a central area of necrosis surrounded by an intermediate cellular zone of radially-arranged mononuclear cells and by a peripheral zone of fibrous tissue,(Fig.43).The necrotic areas were detectable in the stained sections dn naked-eye examination. One area of necrosis was very large and occupied almost half the circumference of the nodule.The nodule was surrounded by a well-defined fibrous capsule.

Continued overleaf....

TABLE 8 (Page 2)

RESULTS OF HISTOLOGICAL EXAMINATION OF 17 SUBCUTANEOUS NODULES

Case	Situation of Nodule	Duration of Nodule (Years)	Diameter of Nodule (cm)	Histological Appearances.
10	Sacrum	½	1½	The structure varies in different parts of the nodule. It consists of areas of necrosis circumscribed by areas of cell infiltration (consisting of fibroblasts, mononuclears, and a few plasma cells); and areas of vascular granulation tissue and corrective tissue. Moderate numbers of mononuclear cells and occasional plasma cells are present in the connective tissue.
17	Ulnar Border (Fig.)	5 weeks	1½	Characteristic structure with one necrotic focus surrounded by radially-arranged mononuclear cells and by corrective tissue. Perivascular infiltration of small blood vessels in the connective tissue with small round cells.
25	Ulnar Border (Fig.)	9/12	1½	Characteristic structure composed of multiple foci consisting of necrosis, radially-arranged, cellular layer and peripheral fibrous tissue. (Fig. 42).

Continued overleaf...

TABLE 8 (Page 3)

RESULTS OF HISTOLOGICAL EXAMINATION OF 17 SUBCUTANEOUS NODULES

Case	Situation of Nodule	Duration of Nodule (years)	Diameter of Nodule (cm)	Histological Appearances.
26	Knuckle (Fig 75)	15	½	Similar to the structure in Case 9 above. In the capsule there is a nodule semi-lunar in shape, consisting of small round cells which are almost all lymphocytes, (Fig. 48). This nodule has a marked resemblance to the inflammatory nodes described in the muscles in rheumatoid arthritis.
26	Ulnar border (Fig 73)	15	2	Similar to the structure in Case 9.
35	Ear (Fig. 39)	9/12	½	Large central area of necrosis surrounded by a vascular granulation tissue. At the edge of a small portion of the necrotic area is a small collection of radially-arranged mononuclear cells.
46	Ulnar border (Fig. 8)	many years	1½	Characteristic structure - almost identical with Case 9 (Fig. 44). 2 of the necrotic foci show a few giant cells with multiple nuclei scattered amongst the radially-arranged layer of mononuclear cells.

Continued overleaf...

TABLE 8 (Page 4)

RESULTS OF HISTOLOGICAL EXAMINATION OF 17 SUBCUTANEOUS NODULES

Case	Situation of Nodule	Duration of Nodule (years)	Diameter of Nodule (cm)	Histological Appearances.
58	Olecranon bursa	6	1	All 3 bursal nodules have a similar structure consisting of multiple foci of necrosis, cellular reaction and fibrous tissue. Some perivascular infiltration of lymphocytes around the smaller blood vessels. At the edges of parts of the nodules is a condensation of flattened cells resembling a bursal lining.
58	Olecranon bursa	6	1	
58	Olecranon bursa (Fig.32)	6	1	
62	Olecranon bursa	1	1	Structure identical with Case 58
67	Ulnar border (Fig.33)			Characteristic structure - very similar to Case 9 (Fig.45)
69	Patella (Fig.38)	3	½	Structure very similar to Case 9. In addition polymorph infiltration is quite marked in the cellular zone.

FIG. 40.

Biopsy of Subcutaneous Nodule from Ulnar Border of Forearm.

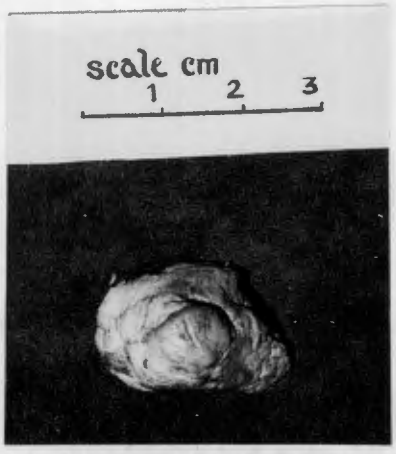
Case 46 : Arthritis Mutilans (Fig. 8).

Low power view of multiple areas of necrosis in the nodule. In one area the necrotic material has folded over on itself. These necrotic foci were recognizable with the naked eye.

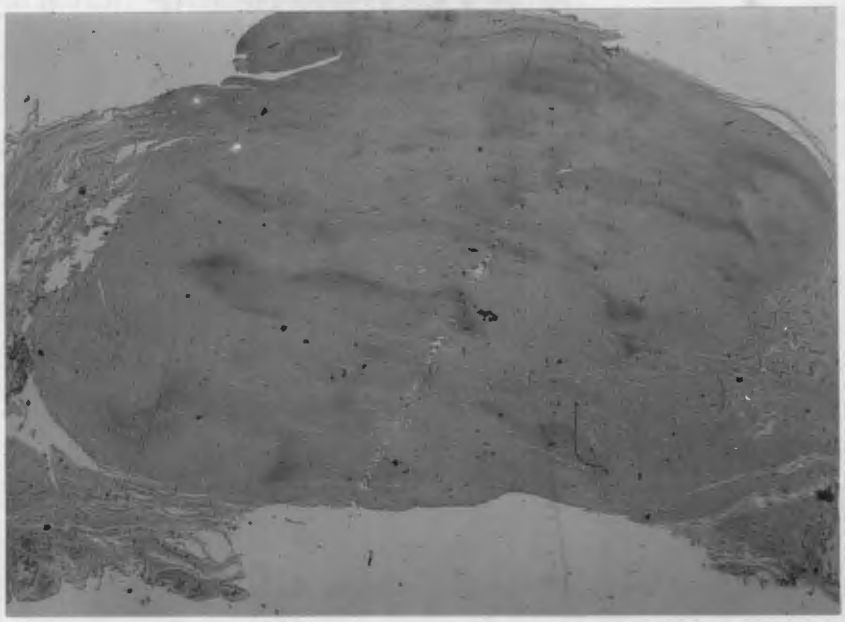
(H. & E. x 10).

FIG. 41.

a.



b.



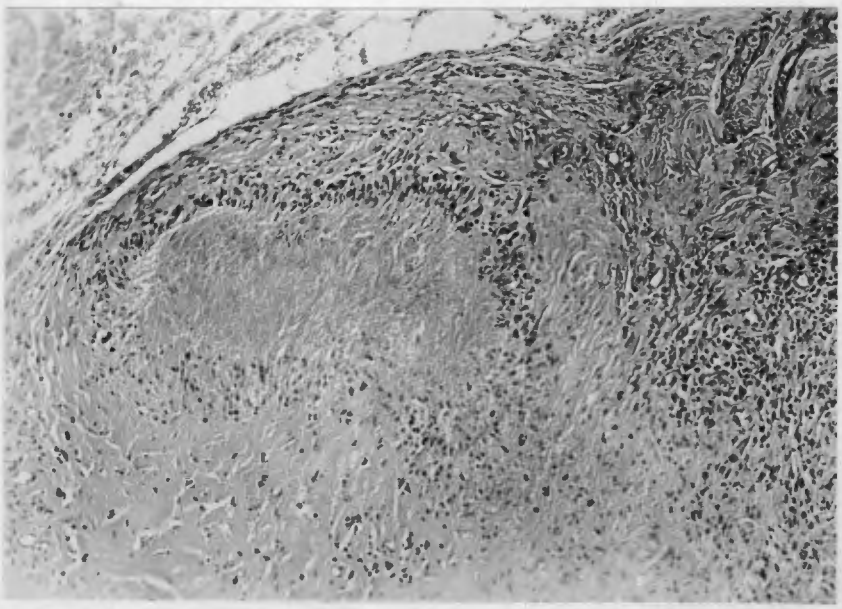
Case 9 : Rheumatoid Arthritis. Pulmonary Tuberculosis.

Fig. (a): Natural size of the nodule after biopsy. Note how it projects from the surrounding connective tissue capsule.

Fig. (b): Low power view illustrating numerous necrotic areas which were recognizable with the naked eye. Note well-defined edge and surrounding connective tissue capsule.
(See Fig. 43 for histology).
(H. & E. x 10).

FIG.42.

Subcutaneous Nodule.



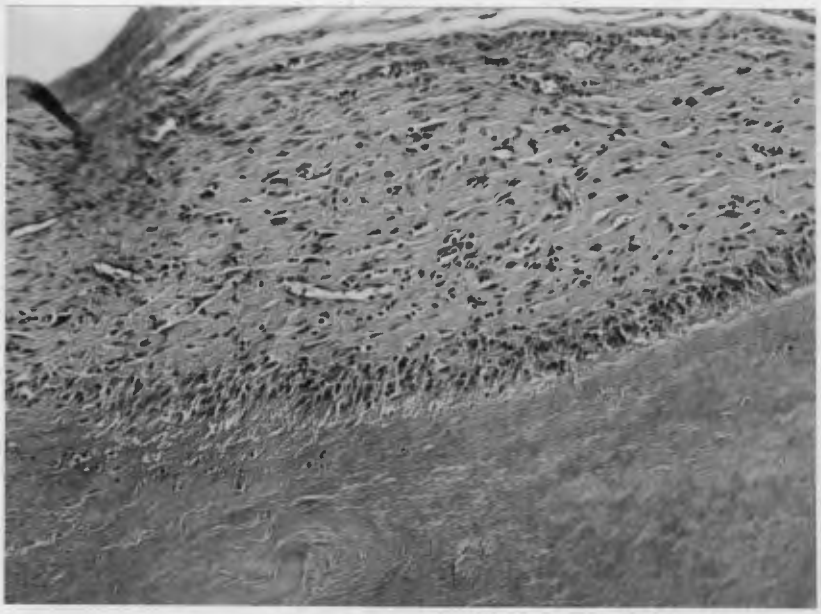
Case 25 : Rheumatoid Arthritis.

Characteristic appearance of focus consisting of necrotic centre, radially- arranged cellular zone and peripheral connective tissue.

(H. & E. x 95).

FIG. 43.

Biopsy of Subcutaneous Nodule from Ulnar Border of Forearm.



Case 9 : Rheumatoid Arthritis. Pulmonary Tuberculosis. (Fig. 28).

Characteristic appearance of a focus with 3 zones:

(i) central zone of necrosis.

(ii) intermediate zone of mononuclear cells with a striking tendency to be arranged radially at right angles to the necrotic area.

(iii) peripheral zone of fibrous tissue.

(See Fig. 28 for photograph of nodule in situ on forearm).

(H. & E. x 130).

FIG. 44.

Biopsy of Subcutaneous Nodule.

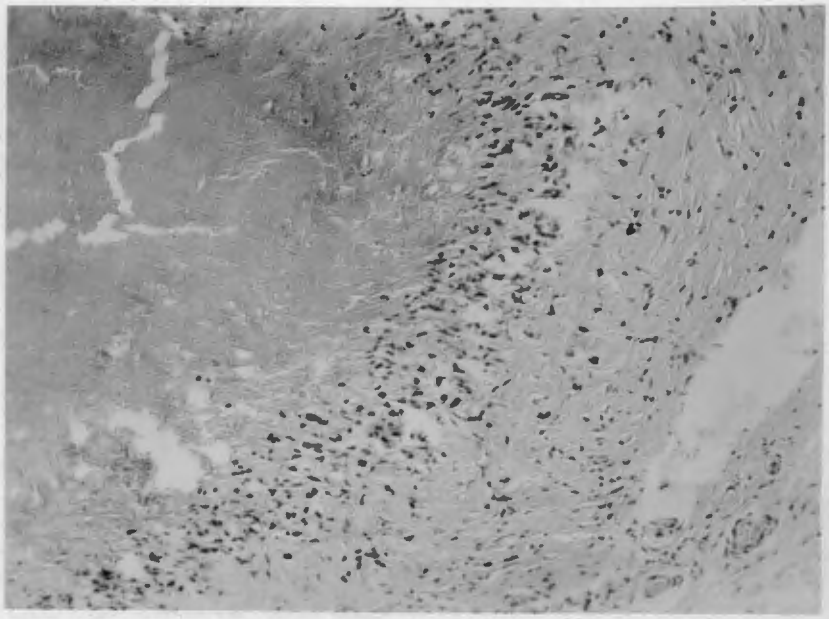
Case 46 : Rheumatoid Arthritis.

Characteristic appearance of a focus with the 3 zones of necrosis, mononuclear cells in pallisade formation and fibrous tissue.

(H. & E. x 130).

FIG. 45.

Biopsy of Subcutaneous Nodule.



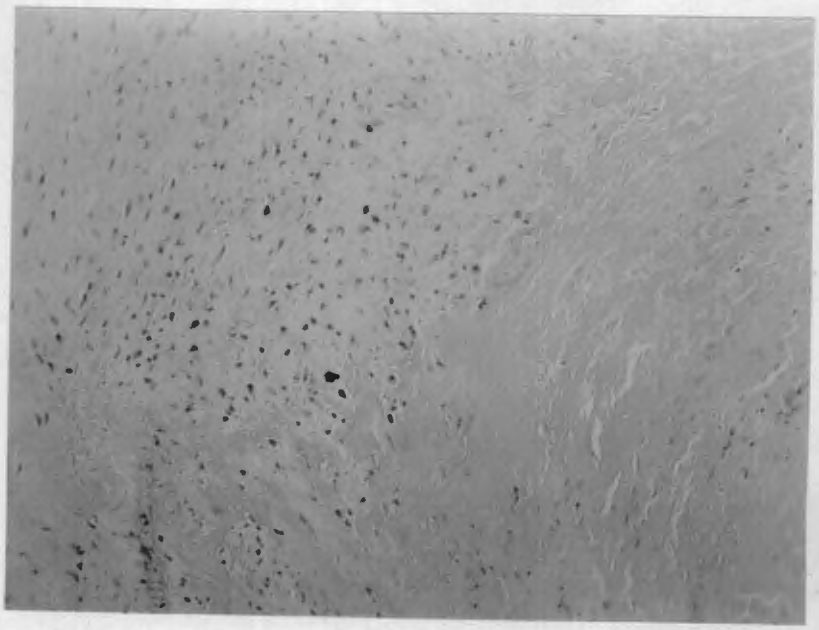
Case: 67 : Rheumatoid Arthritis.

The characteristic 3 zones are detectable but the pallisade formation is less striking than in Figs. 43 and 44 .

(H. & E. x 130).

Fig. 46.

Biopsy of Subcutaneous Nodule.



Case 25 : Rheumatoid Arthritis.

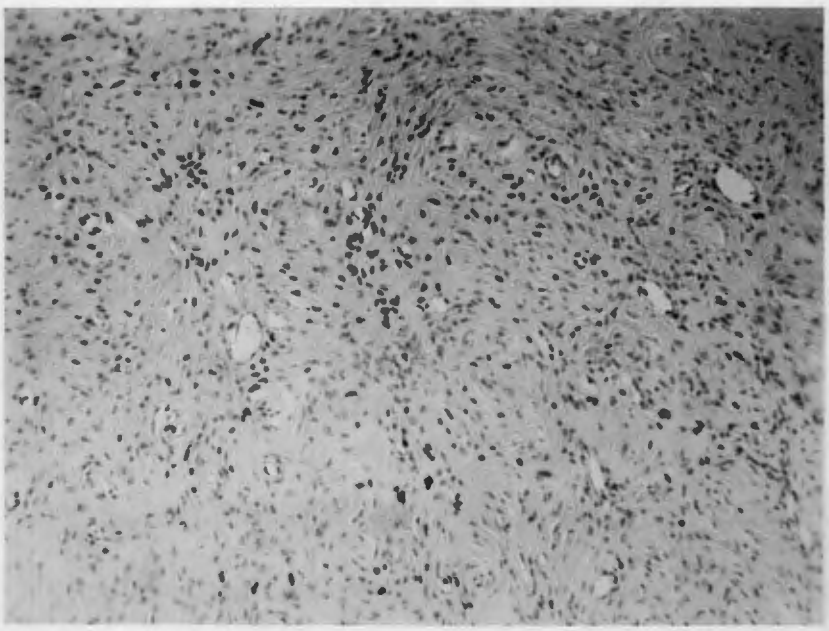
Focus of necrosis adjacent to fibrous tissue without any pallisade formation.

(Cf. with Figs. 43 , 44 and 45).

(H. & E. x 130).

FIG. 47.

Biopsy of Subcutaneous Nodule.



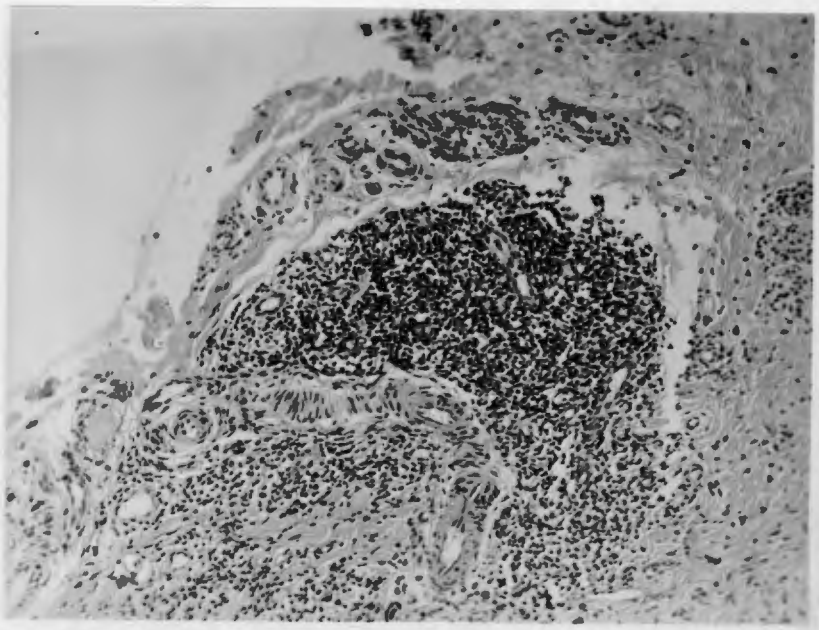
Case 2 : Rheumatoid Arthritis with Aortic Regurgitation (Fig. 83).

No areas of necrosis with palisade formation were noted. The section revealed only fibrous tissue containing fibroblasts and mononuclear cells.

(H. & E. x 130).

FIG. 48.

Biopsy of Subcutaneous Nodule on Dorsum of Interphalangeal Joint.



Case 26 : Rheumatoid Arthritis with Multiple Nodules (Fig. 75).
Nodular collection of small round cells at periphery of a subcutaneous nodule. It closely resembles nodules which may be found in the muscle. (Cf. with Fig. 90).
(H. & E. x 130).

3. Discussion.

The histological features corresponded with those described by DAWSON (1933) and COLLINS (1937). All the nodules (with the exception of Case 2) showed a variable number of characteristic foci.

(a) The necrotic areas in the centre of the foci varied considerably in size. The nodule in Case 4 had a very small area of necrosis, and all grades of necrosis were encountered. In several of the larger nodules the necrotic areas were visible to the naked eye in the stained sections, and could be easily recognized under very low magnification (Figs. 40 and 41). In Case 7 some of the necrotic areas had a "stringy" strandlike appearance similar to the condition termed "fibrinoid degeneration" by DAWSON (1933) and COLLINS (1937); it appears to be an appearance produced by areas which are commencing to undergo necrosis.

(b) The cellular layer completely encircled many necrotic areas, producing a highly

characteristic ...../

characteristic appearance. There was a marked tendency for these mononuclear cells in the intermediate zone to assume a position at right angles to the central necrotic zone. Very striking palisade formations often resulted, e.g. Figs. 43 and 44. In other foci the palisade was less well marked (Fig. 45), and in other foci connective tissue lay adjacent to necrotic foci without an intermediate cellular zone (Fig. 46). In Case 46 several giant cells were present in the cellular layer, and in a few cases there was a moderate number of polymorphs.

(c) The peripheral zone consisted of varying amounts of vascular and of fibrous connective tissue. In some areas the peripheral zone resembled granulation tissue and in other areas it resembled hyaline fibrous tissue. All gradations were detected in some cases. There was

a...../

a variable degree of infiltration by lymphocytes and mononuclear cells in the connective tissues.

Perivascular infiltration of the small vessels in the peripheral zone and in the capsule was noted in several cases. The cells were chiefly lymphocytes.

In the smaller nodule from Case 26 the connective tissue capsule contained a nodular collection of lymphocytes similar in appearance to the inflammatory nodes described in the muscles in rheumatoid arthritis.

The nodules excised from the olecranon bursae usually showed one or more slitlike spaces lined by cells which are closely packed together and so disposed as to resemble a bursal or synovial lining.

It is interesting to note that well marked necrotic foci were present in 2 nodules which were present for only 5 weeks and 3 months. Also marked necrosis was present in some small nodules, e.g. in Case 35 and Case 26. Thus, though the largest areas of necrosis tended to occur in the older and larger nodules, well marked necrosis also occurred in some recent and in some small nodules.

The nodule in Case 2 was removed from the ulnar border of a patient with rheumatoid arthritis and aortic regurgitation (Fig. 82). It was small in size (½ cm. in diameter) and its duration was unknown. It

differed.....

differed from all the other nodules by having no detectable necrotic area. It is possible that the section made did not happen to pass through a necrotic area; or it may be possible that there was no necrosis and that the nodule consisted only of cellular fibrous tissue. (Fig. 47).

In general these histological findings closely conform with those noted in reviewing the literature.

C. NECROBIOTIC NODULES OF RHEUMATOID ARTHRITIS WITH CALCIFICATION.

DAWSON (1933) did not observe the deposition of calcium or of osteoid tissue in any of the cases which he studied. BENNETT, ZELLER and BAUER (1940) noted that the centres of some of the older lesions were calcified. KEIL (1938) stated that although Dawson did not encounter calcification of the necrotic areas, the phenomenon is not rare, and that calcification was found in one instance under his observation and that it has been reported in earlier literature. In rare cases these may apparently even be an attempt at the formation of osteoid tissue. KERSLEY, GIBSON and DESMARAIS (1946) did not describe calcification in any of the nodules they biopsied.

Case Report.

One nodule examined in this series showed extensive calcification.

The patient (Case 56) was a European female aged 70 with chronic rheumatoid arthritis of 4 years duration. The fingers, wrists, elbows, shoulders and knees were chronically painful and swollen. Movements were markedly limited and fibrous ankylosis and deformities had already developed in many joints (including the terminal

interphalangeal....

interphalangeal joints). She was permanently bedridden.

She stated that a painless nodule had appeared over the left elbow a few months after the onset of the arthritis. This subcutaneous nodule was situated over the posterior border of the left ulna 1½" distal to the tip of the olecranon process (Fig. 49). It was stony hard in consistency, very mobile, and was without any attachment to the underlying periosteum. At the biopsy it was removed from the subcutaneous tissue with the greatest facility (Fig. 50). There were no other subcutaneous nodules.

The histology was very interesting. The nodule had a well defined fibrous tissue capsule. A few small areas of necrosis could be seen but the nodule consisted mainly of dense hyaline fibrous tissue. There was no evidence of any radial arrangement of mononuclear cells round the few areas of necrosis. Areas of calcification were prominently scattered throughout the section (Fig.51).

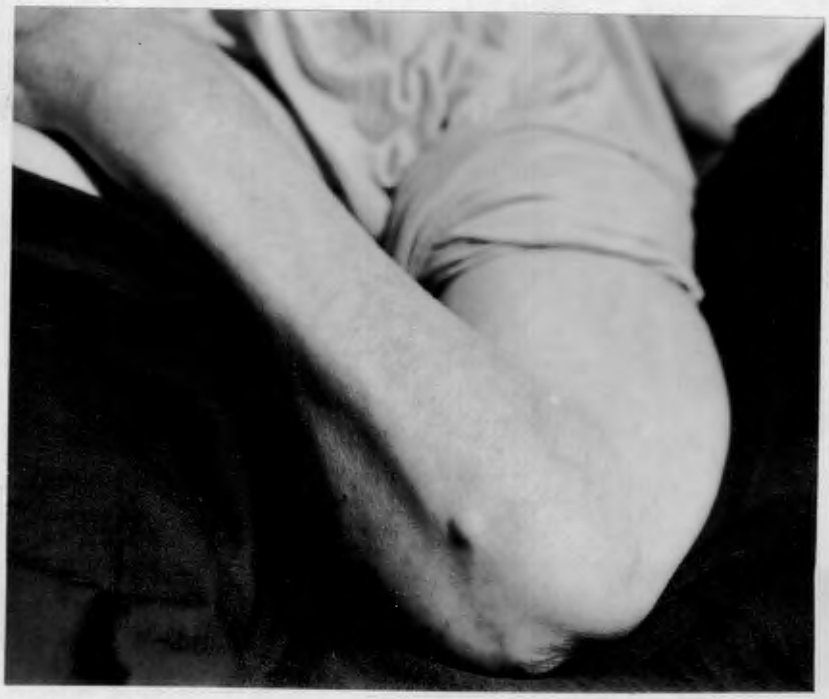
Discussion.

This case is an excellent example of the occurrence of calcification in the subcutaneous nodules of rheumatoid arthritis. It is well known to pathologists that old-standing lipoid necrotic or fibrotic material in various

lesions....

FIG. 49

Calcification of Subcutaneous Nodule in Rheumatoid Arthritis.



Case 56: Chronic Rheumatoid Arthritis.

Small well-defined subcutaneous nodule over ulnar border of left forearm.

FIG. 50.

Calcification in Subcutaneous Nodule.

a.

b.

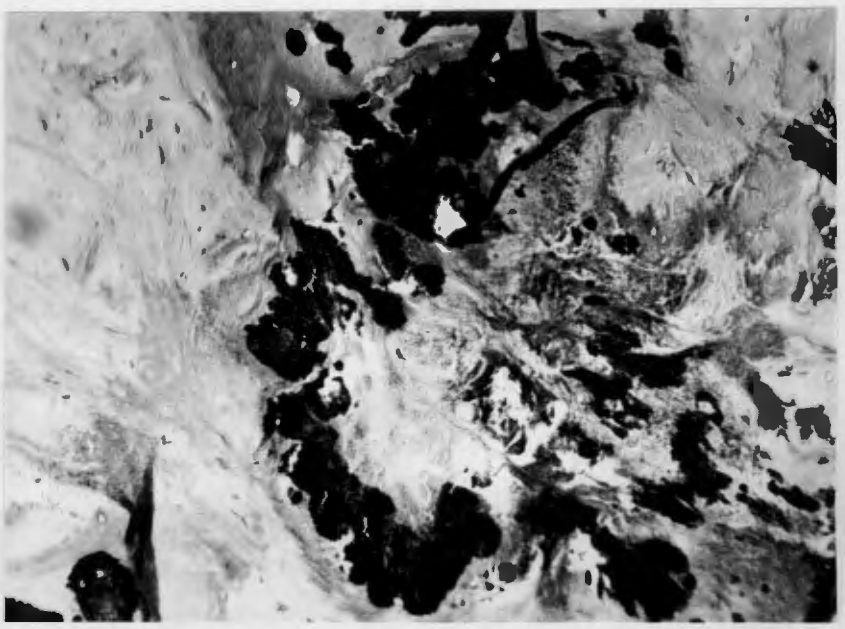
Case 49: Chronic Rheumatoid Arthritis.

Fig. a: Subcutaneous Nodule from left elbow. Well-defined edges.

Fig. b: Areas of calcification in nodule.

FIG. 51.

Calcification in Subcutaneous Nodule.



Case 49 : Rheumatoid Arthritis.

Marked deposition of calcium in the nodule. The shape of the area of calcification suggests that it is at the site of an area of necrosis.
(H. & E. x 130).

lesions in the body may undergo calcification, so it is not surprising that a similar change occasionally occurs in the necrotic areas of these subcutaneous nodules.

Gouty tophi, too, may undergo calcification. Fig. 52 illustrates a case of proved gout with a large calcified tophus in the olecranon bursa. Normally sodium biurate crystals are radiotranslucent and the opacities detectable in the bursa radiologically are the areas of calcification (Fig. 52). This again illustrates that calcification may develop in a variety of conditions.

The most striking feature of the case clinically was the extremely good definition of the edges of the nodule and its very free mobility.

FIG. 52.

Calcification of Olecranon Bursa.

a.

b.

Case 79: Gout.

Fig. a: Large nodular tophus on right olecranon bursa.

Fig. b: Calcification in bursa producing radio-opaque particles (sodium biurate is radio-translucent.)

D. "NECROBIOTIC NODULES OF THE RHEUMATOID ARTHRITIS TYPE WITH LIPOID DEPOSITION."

1. Review of the Literature.

WEBER (1944) suggested the term "Necrobiotic Nodules of the Rheumatoid Arthritis Type" to designate the now well-known characteristic subcutaneous nodules which were described by DAWSON and BOOTS (1930), CLAWSON and WETHERBY (1932), DAWSON (1933), COLLINS (1937) and BENNET, ZELLER and BAUER (1940). He noted that exceptional subcutaneous nodules occur occasionally which differ in histological structure only by the deposition of lipoid material. FLETCHER (1946, 1947) has used the term "Necrobiotic Nodules of the Rheumatoid Arthritis Type with Lipoid Deposition" to indicate this special type of subcutaneous nodule which has been described in rheumatoid arthritis. Weber has written several papers on this subject. They are largely concerned with periodic reports on a case of chronic rheumatoid arthritis which was first demonstrated by Weber and Freudenthal at the Royal Society of Medicine in December, 1936. Further reports were made by Weber in 1943, 1944, 1947 and 1948 on this same case. The result has been that one has had the unique opportunity to follow up a case of great interest over a period of 12 years.

The patient aged 35 in 1936, had rheumatoid arthritis for 6 months. The arthritis was accompanied by multiple subcutaneous nodules over the elbows, the olecranon ridges, the dorsum of the hands, the buttocks, the greater trochanters, the coccyx and over both acromial regions. Numerous smaller nodules were present on the ears and on the face, especially over the borders of the lips and nostril. Some of the subcutaneous nodules were reddish in appearance, others were yellowish-red. They were firm in consistency. None of the nodules were painful or tender with the exception of the nodules over the elbows.

A biopsy of one of the nodules was excised by FREUDENTHAL (1936). The main feature was the presence of large masses of cells forming round or oval areas which were scattered irregularly between the bundles of collagen tissue in all parts of the cutis. These cells were so numerous that their mass exceeded that of the collagen tissue the bundles of which were pressed aside. The cells were conspicuous by their size, which was up to 4 times the size of an epithelial cell. Most of the cells were multinucleated. The cytoplasm was well-stained, well-defined and abundant. It was homogenous and did not have a "foamy" structure. When sections were stained

for fat ...../

fat with Sudan III, these cells in some areas showed no fat nor lipoid at all; in other areas the cytoplasm was stained a faint red. There was "no double refraction".

WEBER (1944, 1947) was uncertain what these cells should be called. He hesitated to call them "Xanthoma cells" as this name usually denotes that the cells are loaded with lipoid droplets, i.e. "foam cells". In the sections the cells showed either no lipoid or lipoid present in a diffuse form. There was no actual proof of the presence of cholesterol. He tentatively suggested that they might be "prexanthoma cells" at an "intermediate stage in development" towards typical "foam cells". His alternative explanation was that the cells were "at the height of their development" but contained some "special lipoid" which was responsible for their peculiar appearance. WEBER (1944, 1947) did not state in his account of the case whether or not there were changes in other parts of the nodule similar to the necrobiotic changes occurring in the "ordinary" subcutaneous nodules, but one understands that such changes were not observed in this case. WEBER (1944) at first designated this case as "a syndrome of rheumatoid arthritis combined with multiple xanthomatous connective tissue infiltrations." The serum cholesterol was 230 mg. per cent and 350 mg.

per cent..

per cent on 2 separate occasions, and was 110 mg. per cent after the patient was treated with a "fatpoor diet".

The patient was next seen in 1941. He still had symptoms due to his arthritis but there were "only remnants of the nodules on the hands and about the elbows". Weber considered that the atrophy or involution of the large nodular infiltrations tended to be more complete than that which occurs in other cases of rheumatoid arthritis. In 1943 the patient had "functionally almost recovered" except for some residual stiffness of the right hip. Nodules were still detectable over the knuckles and the elbows. The latest report was made by Weber in 1948. The patient was back at work, felt quite well, and his weight had risen from 7 to 10 stones. The nodules on the elbows had been spontaneously absorbed, but a number were still present on both hands.

WEBER (1948) has stated that he now prefers to call the patient's illness by the somewhat vague term "Lipoid Rheumatism".

FLETCHER (1946, 1947) has described another case of rheumatoid arthritis with subcutaneous nodules in which there was marked lipoid deposition, but which differed in certain respects from Weber's case. The patient was a male, aged 48. Nodules first appeared 4 years after the

onset of the arthritis. They appeared in very many sites - over the occiput, the scapular spines, the pelvic bones, the elbows, the wrists, the fingers, the greater trochanters, the knees and the feet. There appeared to be about 40 nodules according to the description given. The nodules were "pale" in colour. There was marked deterioration in the general health.

Biopsy examinations were made of 4 nodules situated over the olecranon process, the forearm and the fingers. Widespread necrosis was the most striking feature in all the nodules. One nodule had the histological picture which is usually encountered in the characteristic nodules of rheumatoid arthritis, viz. central necrosis surrounded by mononuclear cells arranged in a palisade manner. Around most of the necrotic areas in the other nodules was a broad cellular band composed of typical "foam cells". The cells were large, pale and contained numerous very distinct vacuoles. These "foam cells" gave a positive Schultze test for cholesterol and showed fine orange-red droplets in sections stained with Sudan. Stained granules could be seen in the cells and filling the spaces between connective tissue bundles. Cholesterol was also demonstrated by the Schultze test in the greater part of the necrosis and in the immediate surrounding

tissues...../

tissues, i.e. it was intracellular and extracellular. Multinucleated giantcells of the "foreign body type" were frequently present. In some nodules the central necrotic zones were surrounded by the characteristic mononuclear cells in palisade manner and by "foam cells". Surrounding the cellular zone of "foam cells" or of mononuclear cells were connective tissue bands which contained numerous lymphocytes, plasma cells and well-defined "foam cells". The bloodvessels in the neighbourhood of the nodules, and in the nodules, often showed inflammatory changes.

Fletcher stressed that the basic histological reactions of focal necrosis, cellular proliferation, round cell infiltration and vascular lesions were present in these nodules, and that they differed from the nodules described by COLLINS (1937) largely in the altered cytology. The essential difference was the presence of cells which showed vacuoles, which contained cholesterol by Schultze's test and which stained decisively with Sudan III.

Fletcher observed that the microscopical appearances of the "foam cells" were not dissimilar from those seen in Weber's case (although Weber avoided using the term "foam cells"). The similarity in the appearances of the "prexanthoma cells" in Weber's case to the "foam cells" ...../

cells" of Fletcher's case is obvious on comparing the photographs. Fletcher suggested the term "Necrobiotic Nodules of the Rheumatoid Arthritis Type with Lipoid Deposition" to describe his case.

The serum cholesterol was recorded twice in Fletcher's case; the results were 135 and 154 mg. per cent.

Weber and Fletcher could find no records of previous descriptions of similar cases in the literature with the possible exception of a case described by LAYANI (1939) and by LAYANI, LAUDAT and ASTRUC (1939). Layani referred to his case as "Xanthomatous Chronic Deforming Rheumatism", and GRAHAM and STANSFELD (1946) have summarized his descriptions. The patient was a female of 46 with chronic polyarthritis of 15 years duration. There was gross disorganization of the joints. She developed xanthoma planum et tuberosum, angina pectoris, prolonged jaundice with hepatomegaly and marked hypercholesterolaemia. There was no autopsy report and it is uncertain what the nature of the disease was. The possibility exists that it was a combination of rheumatoid arthritis with generalized Primary Xanthomatosis and Xanthomatous Biliary Cirrhosis (THANNHAUSER)(1940), but one cannot be certain.

GRAHAM and STANSFELD (1946) have described a case which presented with clinical features of polyarthritis

resembling rheumatoid arthritis. Cutaneous nodules appeared and increased progressively in size and number. Ill-defined nodules also developed in the subcutaneous tissue and in the muscles. Radiological examination revealed patchy bone destruction of many parts of the skeleton.

The histological examination of the nodules revealed widespread involvement of many mesodermal tissues by histiocytes with "foamy" cytoplasm. The microchemical tests for fat, lipoid and glycogen in these cells were negative. After 2 - 3 years a nodule in the right axilla increased rapidly in size and assumed the appearance of a malignant tumour. The patient died and the histological appearances of this tumour were those of a "polymorphic-celled sarcoma". There was extremely widespread infiltration of certain mesodermal tissues by similar cells to those encountered in the original biopsy.

The authors suggested that this case should properly be classed among the lipoidoses, and they referred to it as "a case of a hitherto unrecognized Lipoidosis simulating rheumatoid arthritis".

WEBER (1944) compared his case with Graham and Stansfield's case and noted a few small similarities,

e.g. the ...../

the application of heat appeared to increase the size of the nodules in both cases, and both cases had nodules on the face.

It is obvious, however, that this case has no real resemblance nor relationship at all to Weber's and to Fletcher's cases. It merely simulated rheumatoid arthritis on account of the widespread bony involvement in the same manner that some cases of Boeck's Sarcoidosis do.

2. Case Report.

One case in this series had a subcutaneous nodule with marked lipoid deposition (Case 6).

The patient was an elderly European male aged 78. He was the oldest case in the series and had suffered from chronic rheumatoid arthritis for 43 years. The duration of the disease was thus the second longest in the series. (Case 26 had the disease for approximately 45 years). The proximal interphalangeal joints, metacarpophalangeal joints, wrists, elbows, shoulders and knees were affected. These joints were constantly painful and stiff. He had never experienced a remission since the onset of the disease but the degree of pain and swelling fluctuated. He considered that he was "at his worst" 12 years ago. He lost 15 pounds in weight at the onset but there was no further decrease in weight. Nodules developed painlessly on both elbows approximately 12 years ago. They attained the size of "walnuts" but have since decreased considerably in size.

On examination he was found to be in a fair state of general health. All the affected joints were slightly swollen and slightly tender with limitation of movement. There was some ulnar deviation of the fingers, with wasting of the thenar and hypothenar eminences. There were no gross deformities nor contractures. While he was

under...

under observation during 1947 - 1948 he had an attack of coryza with acute pharyngitis, followed by an exacerbation of the features of the polyarthritis. The affected joints became very painful and more swollen. Several months later he had largely "recovered" from the relapse.

Subcutaneous nodules were present over both elbows. Two nodules were present in the left side, the proximal one being situated over the proximal end of the radius, and the distal one along the posterior border of the ulna, 2" distal to the tip of the olecranon process. (Figs 53 and 54). The nodules were peasized. The nodule over the head of the radius was soft in consistency and was mobile and the nodule over the ulnar border was firm and adherent to the underlying periosteum.

A soft mass was visible and palpable over the right olecranon process in the situation of the olecranon bursa. It consisted of soft tissue and did not fluctuate. In it could be palpated one discrete, firm, peasized nodule and 5 tiny nodules, each the size of a pin's head, which were loosely adherent to each other.

No other abnormalities were noted with the exception of arteriosclerosis and slight hypertension. The urine and the bloodcount were normal.

The diagnosis was confirmed radiologically by the

demonstration ...../

demonstration of characteristic changes in the hands and wrists. Some secondary osteo-arthritic changes were also detected.

The results of the special investigations are summarized below: (TABLE 9)

TABLE 9.

Results of Special Investigations on Case 8.

Sedimentation Rate.	40 mm.
Serum Uric Acid	(i) 3.5 mg. per cent (ii) 3.2 mg. per cent
Serum Cholesterol	139 mg. per cent
Blood Urea	35 mg. per cent
Serum Albumin	4.6 g per cent
Serum Globulin	2.7 g per cent
Thymol Turbidity	7
Colloidal Gold	5
Thymol Flocculation	4
Congo Red Test :	61 per cent of dye remained in serum after one hour.
Fractional Test Meal normal;	-65 $\frac{N}{10}$ Na OH
Wasserman Reaction	negative
and Brucella Agglutination	negative

Biopsy of Subcutaneous Nodule.

The mobile nodule over the proximal end of the radius on the left side was removed. (Fig. 55). Its surface was rounded and smooth and it felt fluctuant. A cross-section showed that it was a cyst-like structure. Its centre contained a large amount of yellow, structureless material which was partially detached from the wall of the nodule (Fig. 56). The yellow, structureless material consisted of characteristic cholesterol crystals and of debris (Figs. 57 and 58). A frozen section showed the presence of large amounts of lipoid in the tissues adjacent to the structureless debris (Figs. 59 and 60).

Fig. 61 illustrates a cross-section under very low power. One of the poles and 2 of the side-walls of the nodule can be seen surrounding an empty space. It is this empty space which was filled with debris and the cholesterol crystals seen in Figs. 57 and 58. 2 other similar but very much smaller spaces can be seen near the pole of the nodule.

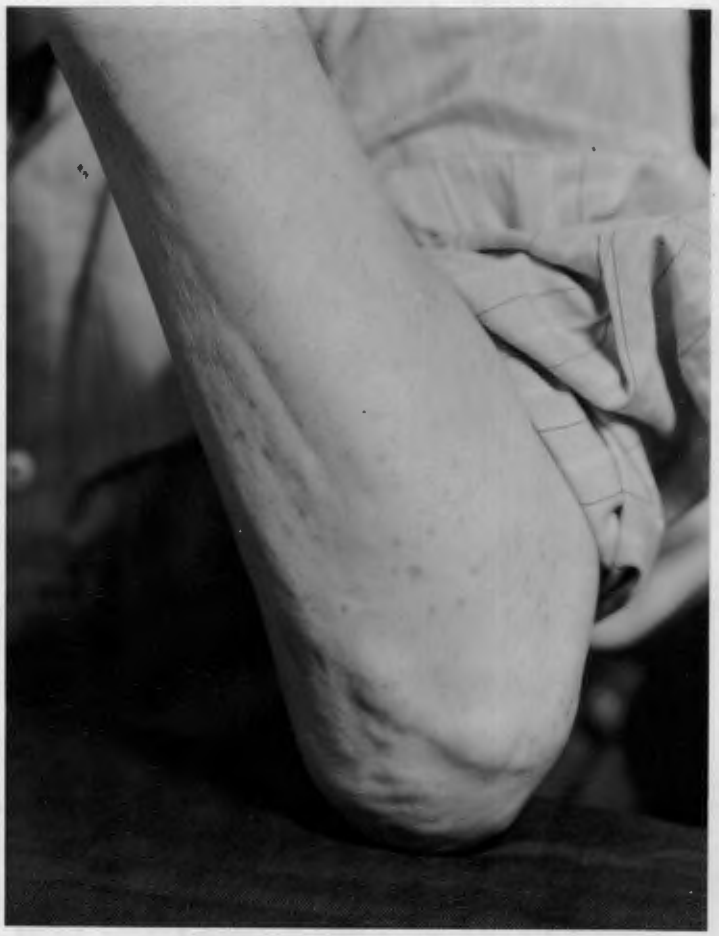
Fig. 62 illustrates a cross-section under a higher magnification. It can be clearly seen that the wall of the nodule is composed of 2 parts:

(a) an outer layer of concentric connective tissue fibres,

and....

FIG. 53.

"Necrobiotic Nodule of Rheumatoid Arthritis Type with Lipoid Deposition".



Case 6: Chronic Rheumatoid Arthritis - 43 years duration.
Left elbow: nodules over proximal end of radius and along ulnar border of forearm.
(See Fig. 54).

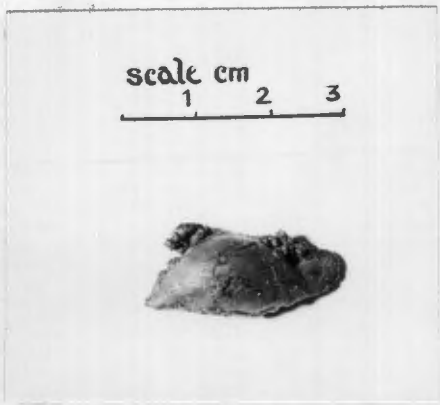
FIG. 54.

"Necrobiotic Nodule of Rheumatoid Arthritis Type with Lipoid Deposition".

Case 6: Chronic Rheumatoid Arthritis.
Lateral view of nodules over left elbow.
(See Fig. 53).

FIG. 55.

"Necrobiotic Nodules of Rheumatoid Arthritis Type with Lipoid Deposition.

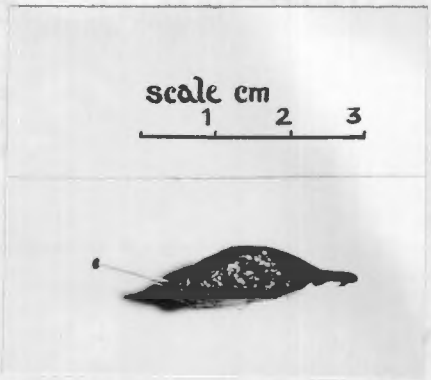


Case 6: Chronic Rheumatoid Arthritis.

Subcutaneous nodule from left elbow. Smooth rounded surface. Fluctuant.

FIG. 56.

"Necrobiotic Nodules of Rheumatoid Arthritis with Lipoid Deposition".

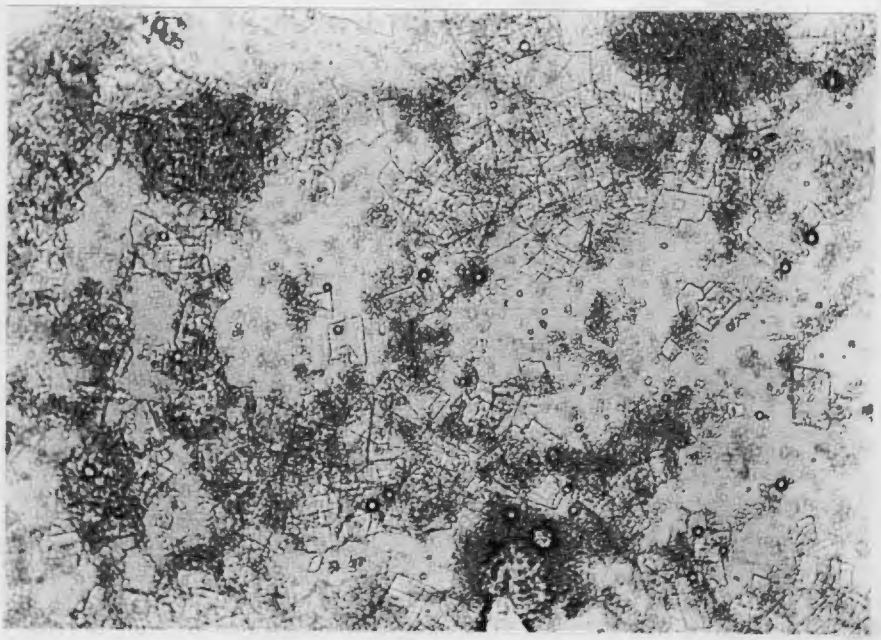


Case 6: Chronic Rheumatoid Arthritis.

Subcutaneous nodule from left elbow consists of fibrous wall with soft yellowish material in the centre, shrinking away from outer wall.

FIG. 57.

"Necrobiotic Nodules of Rheumatoid Arthritis Type with Lipoid Deposition.

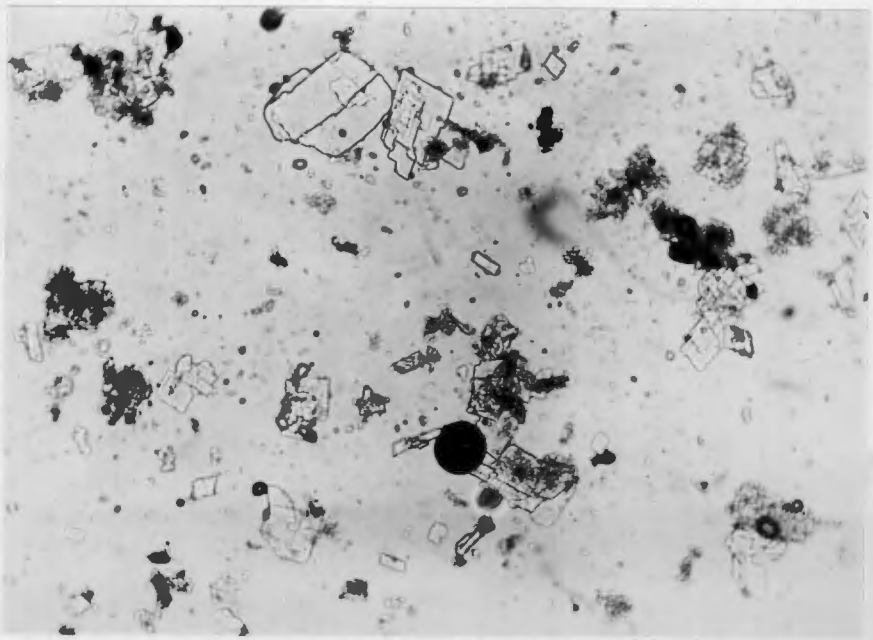


Case 6: Chronic Rheumatoid Arthritis.

Subcutaneous nodule from left elbow. Numerous cholesterol crystals in yellowish material in centre of nodule (Fig. 56).

FIG.58.

"Necrobiotic Nodules of Rheumatoid Arthritis Type with Lipoid Deposition".



Case 6: Chronic Rheumatoid Arthritis.

Subcutaneous nodule from left elbow.

Cholesterol crystals and lipoid droplets in yellowish material in centre of nodule. (See Fig. 56).

FIG. 59.

"Necrobiotic Nodules of Rheumatoid Arthritis Type with Lipoid Deposition."

Case 6: Chronic Rheumatoid Arthritis.

Subcutaneous nodule from left elbow. Outer wall of fibrous connective tissue. Deposition of lipoid in tissues adjacent to central area of cholesterol crystals. (Scarlet Red.)

FIG. 60.

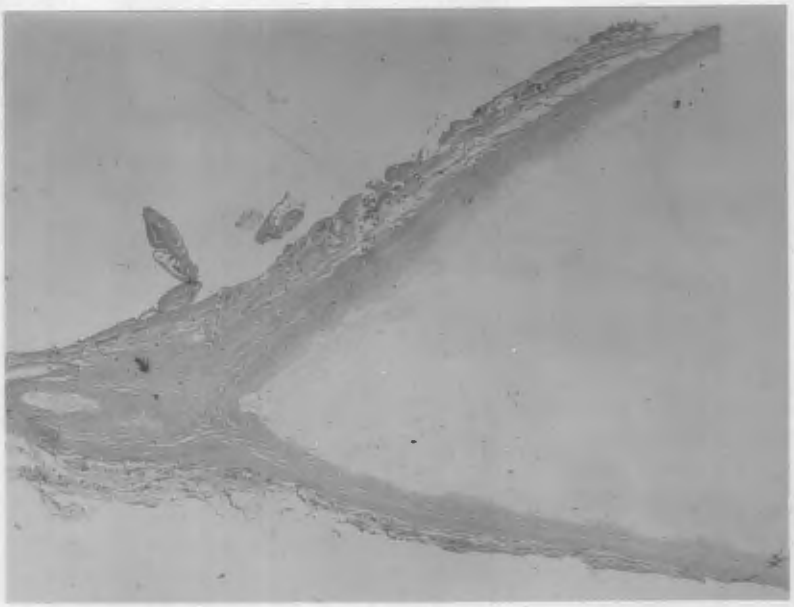
"Necrobiotic Nodules of Rheumatoid Arthritis Type with Lipoid Deposition".

Case 6: Chronic Rheumatoid Arthritis.

Subcutaneous nodule from left elbow. High power view of lipoid in tissue seen in Fig.

FIG. 61.

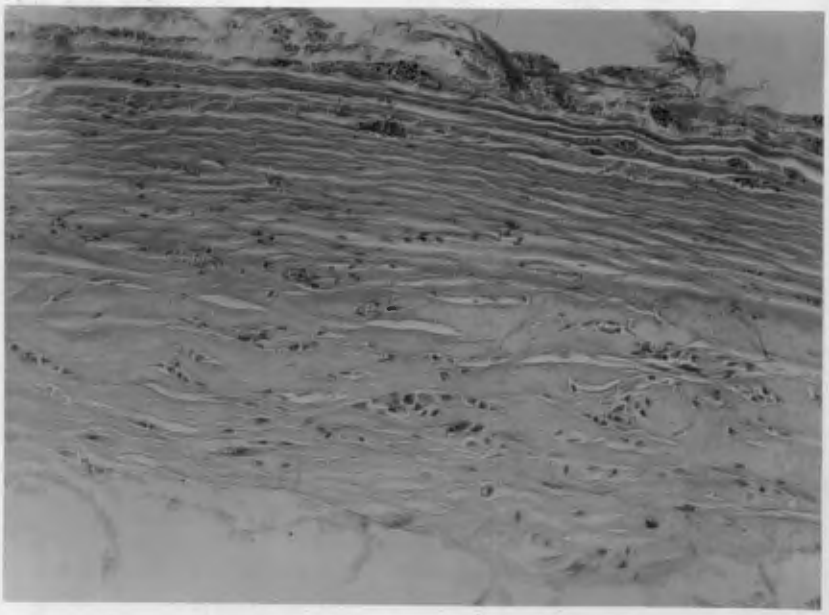
Subcutaneous Nodule of Rheumatoid Arthritis Type with Lipoid Deposition.



Case 6 : Rheumatoid Arthritis.
Low power view of cross-section of nodule. The necrotic centre, the fibrous capsule and the surrounding connective tissue are clearly seen. The large central excavated area is the site occupied by the cholesterol crystals and debris (Fig. 56). At one edge of the nodule smaller excavated areas can be detected. (H. & E. x 10).

FIG. 62.

"Subcutaneous Nodule of Rheumatoid Arthritis Type with Lipoid Deposition.



Case 6 : Rheumatoid Arthritis.

This is a similar section to Fig. stained with haematoxylin and eosin. The fibrous capsule, the area undergoing necrosis and the necrotic debris can be seen. (Cf. Fig. 59).

(H. & E. x 95).

and (b) an inner layer which is undergoing necrosis and degenerating, and which merges with the debris in the centre of the nodule.

A few large foreign-body giant cells were seen at the junction of the inner and outer layers. There were no "foam cells" to be seen.

Some small bloodvessels in the connective tissue at the periphery showed perivascular infiltration with lymphocytes.

3. Discussion.

This case is certainly an example of "lipoid deposition" in a nodule of rheumatoid arthritis. The lipoid deposition was so extensive that it comprised the major part of the nodule. Only a shell of fibrous connective tissue surrounded the large amount of lipoid and cholesterol. From a survey of Figs. 56 - 62 the evolution of the changes which occurred can be imagined. The nodule was of very long duration (12 years) in a case of chronic rheumatoid arthritis. The original areas of necrosis probably underwent liquefaction and lipoid material was deposited. The liquefaction and lipoid deposition proceeded to such an extent that the lipoid

came.....

came to occupy the entire centre of the nodule with a rim of fibrous tissue around it. The 2 small spaces seen in Fig. 61 are probably of a similar nature.

The problem arises as to the relationship of this case to those described by WEBER (1937, 1944, 1947); by FLETCHER (1946, 1947); and by GRAHAM and STANSFELD (1946). It has already been noted that Graham and Stansfeld's case was of an entirely different nature and has no relationship to the other cases, even though it is usually mentioned by authors discussing lipoid changes in rheumatoid arthritis nodules.

The microscopical appearances of this nodule are neither like those of Weber's case nor of Fletcher's case, as no "prexanthoma cells" or "foam cells" were seen.

The nodule appears to be more similar to some of the nodules noted by KERSLEY, GIBSON and DESMARAIS (1946). These workers described various lipoid changes in 3 nodules of rheumatoid arthritis. It is interesting to note the features of each of their nodules. The main features were as follows:

(1) The nodule from their 12th. case had a typical histological appearance in part of the tissue, characteristic of the "usual" necrobiotic nodule. Elsewhere in the nodule the structure was quite different.

The ...../

The central necrotic zone was heavily infiltrated by cholesterol, and the material yielded abundant cholesterol crystals when it was scraped. Foreign-body giant cells were seen in the tissues adjacent to the areas of lipoid infiltration, and appeared in some cases to be attempting to engulf adjacent cholesterol. No "foam cells" were seen. The surrounding fibrous tissue was more hyaline and less cellular than elsewhere.

This nodule thus has many striking similarities to the nodule illustrated in Figs. 55 - 62 . The only difference is one of degree; the lipoid infiltration in the case described by the authors is still restricted to certain areas of the nodule, whereas the lipoid infiltration in the case above (Case 6) is so extensive that it has practically replaced the entire nodule. Both nodules have the same surrounding hyaline fibrous tissue, and a few foreign-body giant cells were noted in both.

(ii) The nodule from their 13th case showed a characteristic necrotic focus in one small area. The rest of the nodule consisted of 2 foci of cholesterol surrounded by numerous layers of dense hyaline eosinophilic fibrous tissue. Perivascular and paravascular cell infiltrations were noted in the fibrous tissue and in the subcutaneous tissue.

This..

This nodule has certain resemblances to the nodule of Case 6, but it has a small central area of cholesterol and a thick surrounding wall of fibrous tissue, whereas the nodule of Case 6 has a large central area of cholesterol and a thinner fibrous tissue wall.

(iii) The nodule from their 14th. case was a "sausage-shaped" mass, which consisted of a fibrous capsule enclosing a "soft yellow greasy necrotic material". Sections showed, in addition to granular amorphous debris, areas of "foam cells". These "foam cells" were large, rounded or polygonal cells with small darkly stained nuclei and well-defined cell membranes. The cytoplasm was vacuolated.

The macroscopic description of this nodule bears a striking resemblance to the features noted in Case 6 - with the important exception of the presence of numerous "foam cells" in their case. These "foam cells" were similar to the cells noted by Fletcher in his case.

On reviewing the cases described by Weber, by Fletcher and by these 3 authors, it seems that a variety of lipoid changes may occur in these subcutaneous nodules of rheumatoid arthritis, and Case 6 is important as it helps to illustrate the "chain" of events which may be occurring...../

occurring.

The problem becomes simplified if one postulates that the primary change is the deposition of a small amount of cholesterol or lipoid in the central necrotic area of a focus in the nodule. DAWSON (1933) had noted that cystic degeneration sometimes occurred in the necrotic areas of oldstanding nodules, and was sometimes followed by the deposition of numerous cholesterol crystals. The subsequent appearance of the nodule probably depends merely on the amount of cholesterol and lipoid which is deposited; on the site of deposition and on the reaction of the surrounding tissues to the presence of the amorphous debris which results from the disintegration of the areas of necrosis.

Thus, any or all of the following changes could conceivably occur: presence of cholesterol crystals in small, moderate or large numbers; presence of foreign-body giant cells in variable numbers; and presence of "foam cells" containing cholesterol and lipoid in variable amounts. The resulting macroscopic and microscopic appearance of the nodule would depend on the extent to which these changes had occurred. Thus:

(a) In Weber's case the lipoid was situated intracellularly, producing cells somewhat resembling "foam cells".

(b) In Fletcher's case the lipoid and cholesterol were situated partly intracellularly producing

"foam" ...../

"foam cells" and partly extracellularly in the connective tissue;

(c) In the 13th. case (in the series of Kersley, Gibson and Desmarais) the extracellular cholesterol deposition formed a small focus surrounded by dense fibrous tissue;

(d) In their 12th. case, the cholesterol was deposited extracellularly in some of the necrotic areas;

(e) In their 14th. case there was extensive lipoid deposition intracellularly, producing "foam cells"; and extracellularly, producing a large area of "soft, yellow greasy material" in the centre of the nodule and (b) in this case Case 6 in this series there was a very extensive extracellular deposition of cholesterol and lipoid, which attained such a great size that it comprised more than three-quarters of the entire nodule. There was no intracellular deposition and no "foam cells" were noted.

If this theory is accepted, it will link together all these cases with their variable degrees of cholesterol and lipoid deposition.

The ...../

It is of interest to note that "lipoid deposition" may occur in gouty tophi. CHAUFFARD and TROISIER (1921) described the presence of cholesterol in tophi, and KERSLEY, GIBSON and DESMARAIS (1946) have noted the presence of "foam cells" containing cholesterol in a tophus of one of their cases with gout. They remarked on the resemblance of the "foam cells" of their case to the "foam cells" described by FLETCHER (1946, 1947) in the nodule of a case of rheumatoid arthritis.

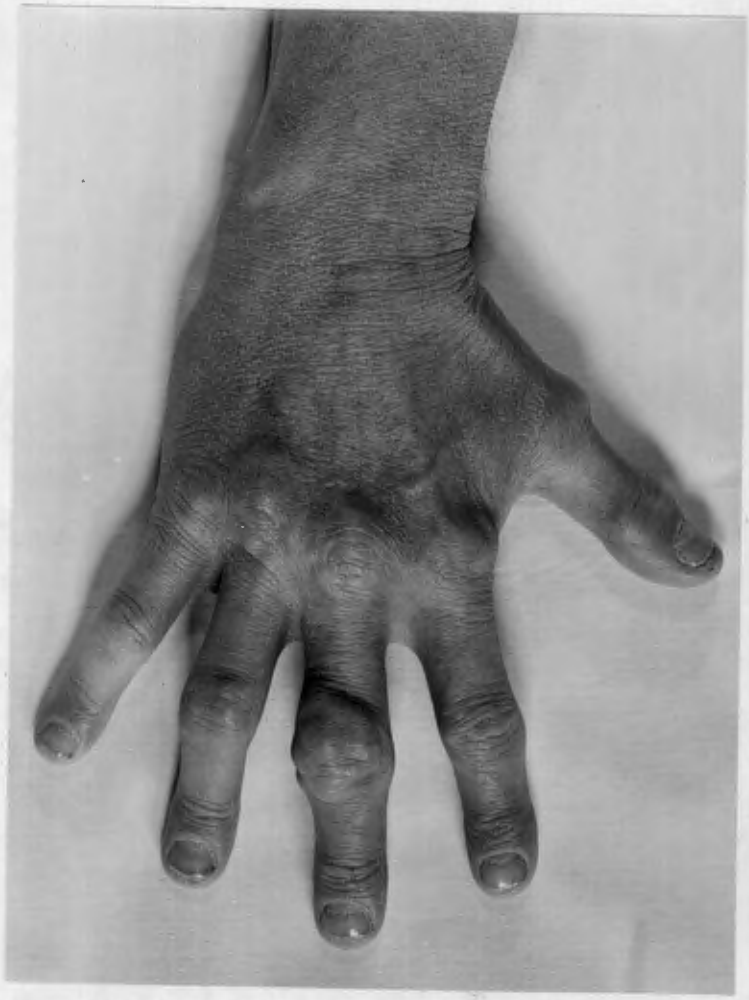
Case 80 - a case of gout (Fig. 63) - was examined in 1941, 1945 and 1948. Some tophi were removed for examination and were found microscopically to contain urate crystals and lipoid material. The diagnosis was made of "gout with xanthomatosis". However, in view of the findings of CHAUFFARD and TROISIER and of KERSLEY, GIBSON and DESMARAIS, it seems more advisable to regard the case as another example of "gout with lipoid deposition".

The occurrence of cholesterol and lipoid deposition in gouty tophi, and the presence of "foam cells" in the case described by KERSLEY, GIBSON and DESMARAIS, lends further support to the hypothesis put forward to reconcile the diverse findings with regard to lipoid deposition in rheumatoid arthritis nodules. If both free cholesterol crystals and "foam cells" can occur in

a gouty ...../

FIG. 63.

Gout with "Lipoid Deposition".



Case 80: Intra-articular tophi.
Lipoid present in some tophi.

a gouty tophus, then it is understandable that either, or both together, might occur in rheumatoid arthritis nodules and produce a variety of histological appearances.

The suggested conclusion is that the "special" nodules described by Weber and by Fletcher are merely interesting variants of a fairly common pathological process - the deposition of lipoid in necrotic areas.

4. EXAMINATION OF SUBCUTANEOUS NODULES FOR THE PRESENCE OF LIPOID.

The nodule in Case 6 was the 10th. nodule in the series which was examined. After the marked deposition of lipoid was noted it was decided to make routine examinations of the nodules for the presence of lipoid in the future. Thus frozen sections from an additional 9 nodules were stained with Scarlet Red in the same manner and examined.

The results were striking and interesting. Of the 9 nodules examined there was a large amount of lipoid in 6 cases; a slight amount of lipoid in 2 cases; and no lipoid in one case. There was thus a High incidence of lipoid in the rheumatoid arthritis nodules as determined by this technique (Table 10).

The distribution of the lipoid was confined to the areas of necrosis. Usually the lipoid was found in the peripheral part of the areas of necrosis (Fig. 64), and occasionally the lipoid was present in the peripheral and central parts of the necrotic areas (Fig. 65). All these 8 nodules in which lipoid could be detected had the characteristic histological appearances with multiple necrotic foci when examined after staining with haematoxylin and eosin; whereas the one nodule which contained

no ...../

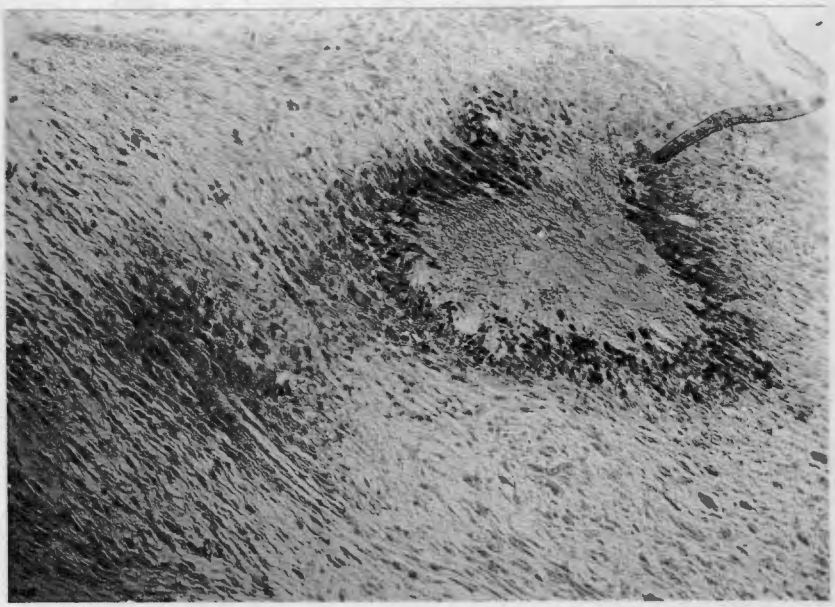
TABLE 10.

RESULTS OF EXAMINATION FOR PRESENCE OF LIPOID IN 9 SUBCUTANEOUS NODULES.

Case	Situation of Nodule	Duration of Nodule (years)	Size of Nodule (cm)	Lipoid
4	Olecranon process	?	½	Absent
9	Ulnar border	1 - 2	1	Large amount (Fig. 64)
17	Ulnar Border	5 weeks	1½	Large amount
25	Ulnar border	9/12	1½	Large amount
35	Ear	9/12	½	Slight amount
58	Olecranon bursa.	6	1	Large amount (Fig. 65)
58	Olecranon bursa.	6	1	Large amount
58	Olecranon bursa.	6	1	large amount
62	Olecranon bursa.	1	1	slight amount

FIG.64.

Lipoid Deposition in Subcutaneous Nodules.

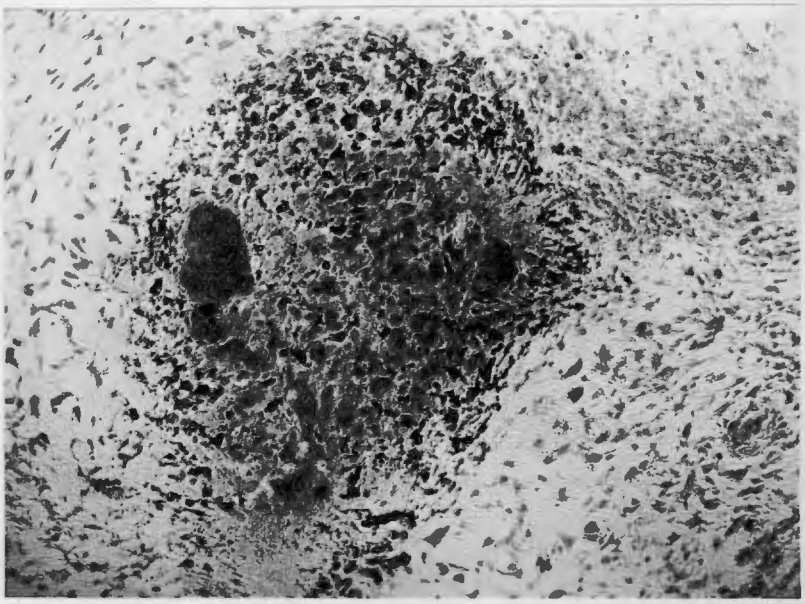


Case 9 : Rheumatoid Arthritis.

Note the marked deposition of lipoid in an area which corresponds to the perimeter of an area of necrosis.
(Cf. with Fig. 65).
(Scarlet Red x 95).

FIG. 65.

Lipoid Deposition in Subcutaneous Nodules.



Case 58 : Rheumatoid Arthritis.

Deposition of lipoid throughout a rounded area which corresponds to the size and shape of an area of necrosis.
(Scarlet Red x 95.)

no lipoid (Case 4) consisted almost entirely of connective tissue with only a minute area of necrosis when examined in the same way. The occurrence and the distribution of the lipoid are therefore closely related to the presence and distribution of the necrotic foci in the nodules. It is interesting to note that the small nodule in Case 17 showed necrosis and lipoid deposition although its duration was short - 5 weeks. In general, the larger nodules tended to have more lipoid than the smaller nodules, with the exception of Case 62, which was 1 cm. in diameter but had only a slight amount of lipoid.

The 6 nodules containing easily recognisable lipoid were removed from the olecranon process in 3 cases and from the ulnar border in 3 cases. The presence of the lipoid was thus noted in nodules which originated outside the olecranon bursa as well as in nodules which originated in, or were attached to, the olecranon bursa.

It has therefore been demonstrated that lipoid is frequently deposited in the necrotic areas in the nodules of rheumatoid arthritis. It was the rule, not the exception, for such nodules to contain lipoid and lipoid was detected in large amounts in 6 out of 9 consecutive nodules.

With the knowledge of the high incidence of lipoid present in the nodules, it appears very

probably ...../

probable that the lipoid can increase in extent as the necrotic areas merge and coalesce with each other. Ultimately the lipoid could occupy a large part of the nodule. "Foam cells" might appear if the lipoid was intracellular. Cholesterol crystals might be demonstrable by scraping and examining the material. Thus the lipoid deposition, which occurs frequently - or at least sometimes - in the necrotic areas, is almost certainly the starting point in the evolution of the nodules described by WEBER (1944); by FLETCHER (1946, 1947); and by KENSLEY, GIBSON and DUSMARAIS (1946); and in the evolution of the nodule described above in Case 6.

The results of the investigation therefore tend to support strongly the suggestions offered of the pathogenesis of the nodule in Case 6 and of similar nodules described in the literature.

The serum cholesterol was within normal limits in all the cases in this series which had nodules, irrespective of whether lipoid was demonstrated in

the ...../

the nodules or not. The serum cholesterol was within normal limits in Fletcher's case and it was slightly raised on one occasion in Weber's case.

These findings are not surprising as the local deposition of cholesterol in various conditions (e.g. in hydrocoele fluid or in hydatid cysts) is neither due to, nor dependent on, hypercholesterolaemia.

E. COMPARISON OF NODULES OF RHEUMATOID ARTHRITIS WITH NODULES OF OTHER DISEASES.

1. Rheumatic Fever Subcutaneous Nodules.

It is not proposed to discuss the relationship of the subcutaneous nodules of rheumatoid arthritis to those seen in rheumatic fever. Clinically the differentiation is usually easy as the nodules of rheumatic fever are smaller; often appear in multiple sites more or less simultaneously and only last several weeks or a few months at most. They have no special predilection for the ulnar border of the forearm and are most commonly encountered on the occipital region. They are probably always a sign of activity. The differentiation of rheumatic fever nodules from recent small nodules of rheumatoid arthritis may not be easy, but there is little difficulty in distinguishing the characteristic rheumatic fever nodule from the characteristic rheumatoid arthritis nodule.

KEIL (1938) has fully reviewed the histological resemblances and dissimilarities between these 2 types of subcutaneous nodules. DAWSON (1933), in a well illustrated paper, endeavoured to show that the 2 types of nodules represented different phases of the same, fundamental pathological process. On the other hand, COLLINS (1937) claimed that the microscopical differentiation of the 2 types of nodules could <u>almost</u>

always...../

always be made, except in the earliest stages. BENNETT, ZELLER and BAUER (1940) agreed with Collins' views and stated that the nodules of rheumatoid arthritis and rheumatic fever differ "as much from one another as do the granulomas of syphilis and tuberculosis"!

The conclusion appears to be that the changes in very early nodules of rheumatoid arthritis may resemble the features seen in rheumatic fever - but the necrotic focus and striking radially-arranged cellular reaction of the older nodules in rheumatoid arthritis present a characteristic appearance which does not occur in rheumatic fever nodules. Grosser secondary pathological changes, such as depoeition of lipoid or calcification, do not appear to occur in rheumatic fever nodules. ZELLER and BAUER (1940) appeared to summarize the problem best by stating that differentiation is usually possible because one or more of the pathological alterations usually predominates, e.g. "fibrinoid degeneration" and oedema predominate in rheumatic fever nodules and "complete necrosis and degeneration" and "palisading" predominate in rheumatoid arthritis nodules.

2. Tophi.

Figs. 66 and 67 illustrates the characteristic distribution of tophaceous deposits on the hands and feet of 2 cases of gout. These tophi were intra-articular and projected out of the joints into the surrounding tissues. The distribution and clinical features of gouty tophi are too well-known to require further discussion, but there are 2 points in the clinical differentiation of tophi from rheumatoid arthritis nodules which were well illustrated in the series of cases of these diseases.

(a) Tophi...../

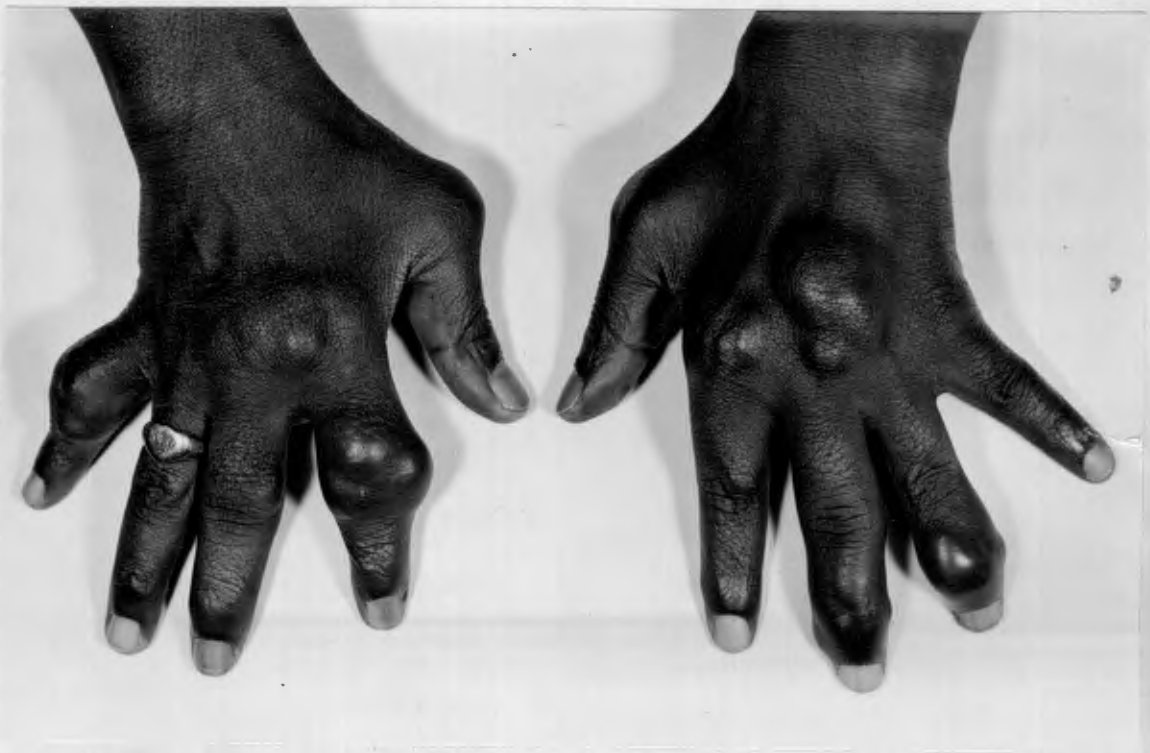
(a) Tophi on the hands and feet are usually asymmetrical, or if occasionally symmetrical are then usually unequal in size; whereas the subcutaneous nodules of rheumatoid arthritis are characteristically symmetrical in the majority of cases (Figs. 36, 37, 72, and 75). Exceptions occur but this feature is of some clinical value.

(b) The rheumatoid arthritis nodules are most commonly situated on the ulnar border of the forearm, 1" - 2" distal to the tip of the olecranon process, and thus the presence of subcutaneous nodules in this site is highly suggestive of the diagnosis of rheumatoid arthritis. It is usually accepted that there is no special tendency for subcutaneous tophi to occur at this site. However it was found that 2 of the 11 cases of gout which were examined had subcutaneous nodules at this very site, (Cases 83 and 84). The diagnosis of gout was demonstrated irrefutably by the presence of sodium biurate crystals in these nodules whb h were thus examples of tophi occurring at the site usually affected by rheumatoid arthritis nodules! Nodules along the ulnar border of the forearm in this situation can thus not be regarded as pathognomonic of rheumatoid arthritis.

In Case 84 the nodules were bilateral. They were fluctuant and sodium biurate crystals were obtained on aspiration....

Fig. 66.

T o p h i.

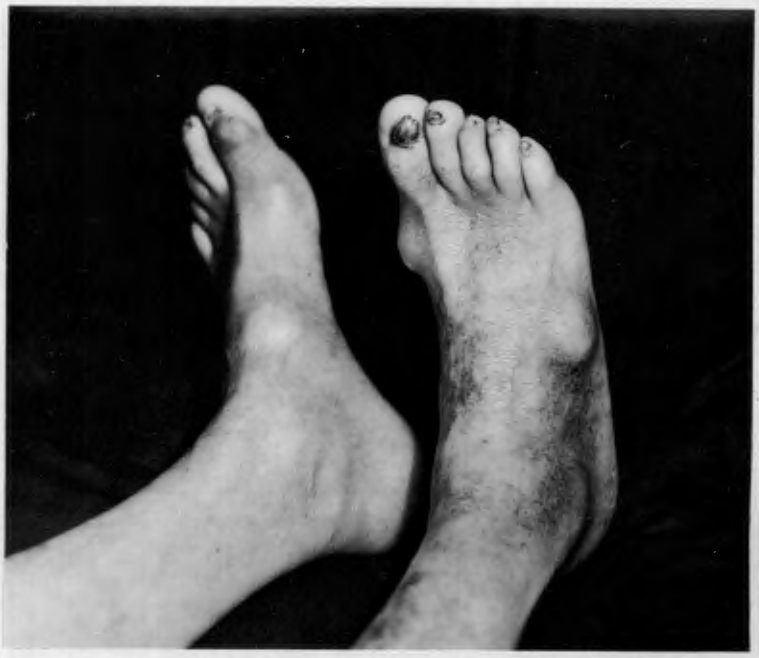


Case 82: Gout.

Large tophi in joints of hands.
Asymmetrical.

FIG.67.

T o p h i.

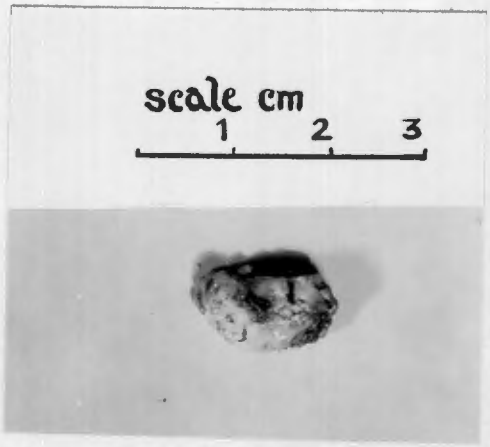


Case 81 : Gout.

Large tophi in joints of feet and toes.

FIG. 68.

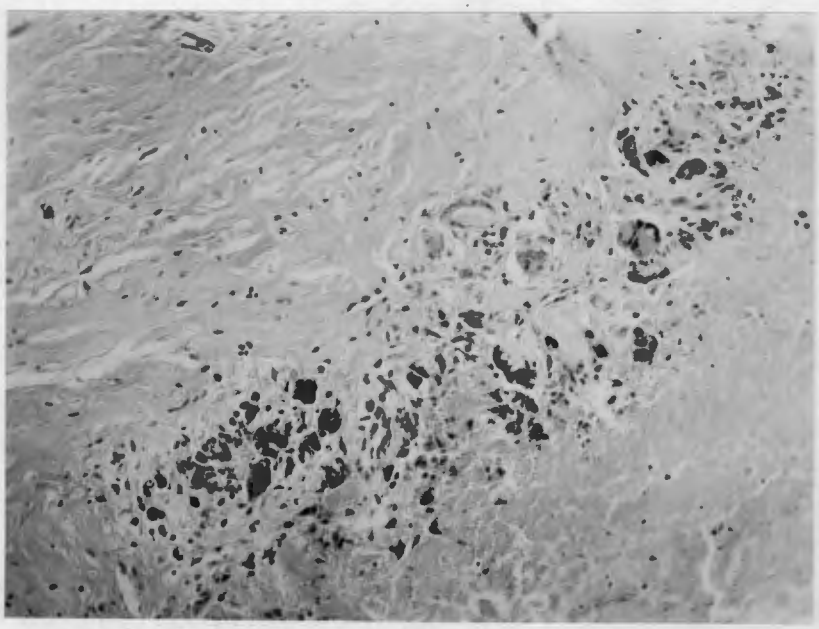
T o p h u s.



Case 83: Gout.
Tophus which was situated in subcutaneous tissue over ulnar border of forearm, 1½" distal to tip of olecranon process.
(See Fig. 69 for histology).

FIG.69.

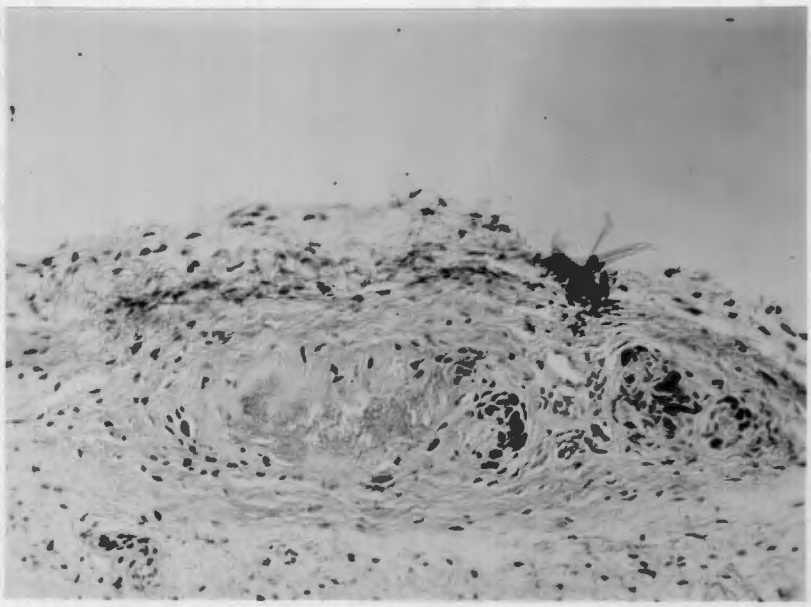
Biopsy of Nodule on Ulnar Border of Forearm
T o p h u s. (Fig. 68)



Case 83 : Gout.
3 zones are detectable: (i) a central necrotic area surrounded by (ii) numerous giant cells and several mononuclear cells and (iii) a peripheral zone of fibrous tissue.
This is the histological appearance of the nodule which was situated in the characteristic position at which rheumatoid arthritis nodules occur. (See Fig. 94 for muscle biopsy from same case)(Cf. Fig. 70 from another case of gout).

FIG. 70.

Biopsy of Nodule on Finger (Tophus).



Case 85 : Gout.

Characteristic appearance of tophus with necrotic area, numerous adjacent giant cells and surrounding fibrosis.

FIG. 71.

T o p h i.

Case 84: Gout.

Subcutaneous nodules along ulnar border of forearm in identical site at which rheumatoid arthritis nodules occur. Diagnosis of gout proved by demonstration of sodium biurate crystals on aspiration of one of these tophi.

aspiration. (Fig. 71)

In Case 83 the nodule was unilateral (right side). It was firm in consistency and felt exactly like a rheumatoid arthritis subcutaneous nodule (Fig. 68). During the biopsy of the nodule it was found to contain obvious crystalline material. Microscopy confirmed the presence of sodium biurate and the Murexide test was positive. The histological structure of the nodule (after the usual fixation and staining) is illustrated in Fig. 69 . The typical features of tophi were present, including numerous foreign-body giant cells.

3. Xanthoma tuberosum et planum.

A striking resemblance was noted between the distribution of the subcutaneous nodules of rheumatoid arthritis and the xanthomatous nodules found in the skin and the tendons in Primary Hypercholesterolaemic Xanthomatosis

The distribution of the nodules is often very similar in the 2 diseases, e.g. over the olecranon process; on the extensor surface of the fingers; in the extensor tendons of the hands and feet; in the tendons above the ankle joints in the distal third of the leg; and in the tendo Achilles. Moreover the nodules are characteristically symmetrical in both diseases, especially when they are situated on the elbows. The

subcutaneous....

subcutaneous nodules in rheumatoid arthritis, especially those large ones over the olecranon processes, are sometimes slightly yellowish in colour and may be erroneously diagnosed as true xanthomata.

It was the remarkable resemblance between the nodules in a case of rheumatoid arthritis and in a case of xanthomatosis which originally aroused interest in the problems of these nodules and led to this thesis. (Cases 26 and 89). Figs. - illustrate the similarities in the distribution and appearances of the 2 types of nodules.

It should be noted that there is no special tendency for xanthomata to occur along the ulnar border of the forearm distal to the olecranon process.

No attempt will be made in this thesis to discuss the clinical and pathological differential diagnosis of the rheumatoid arthritic subcutaneous nodules from the numerous other examples of subcutaneous nodules in various diseases. KKIL (1936) has discussed the features of "fibrositic nodules"; subcutaneous nodules of polyarteritis nodosa; and the juxta-articular nodules of syphilis. Some of Hopkins' cases of syphilitic juxta-articular nodules also had rheumatoid arthritis, which may have been responsible for the nodule formation (1931).

WEBER.....

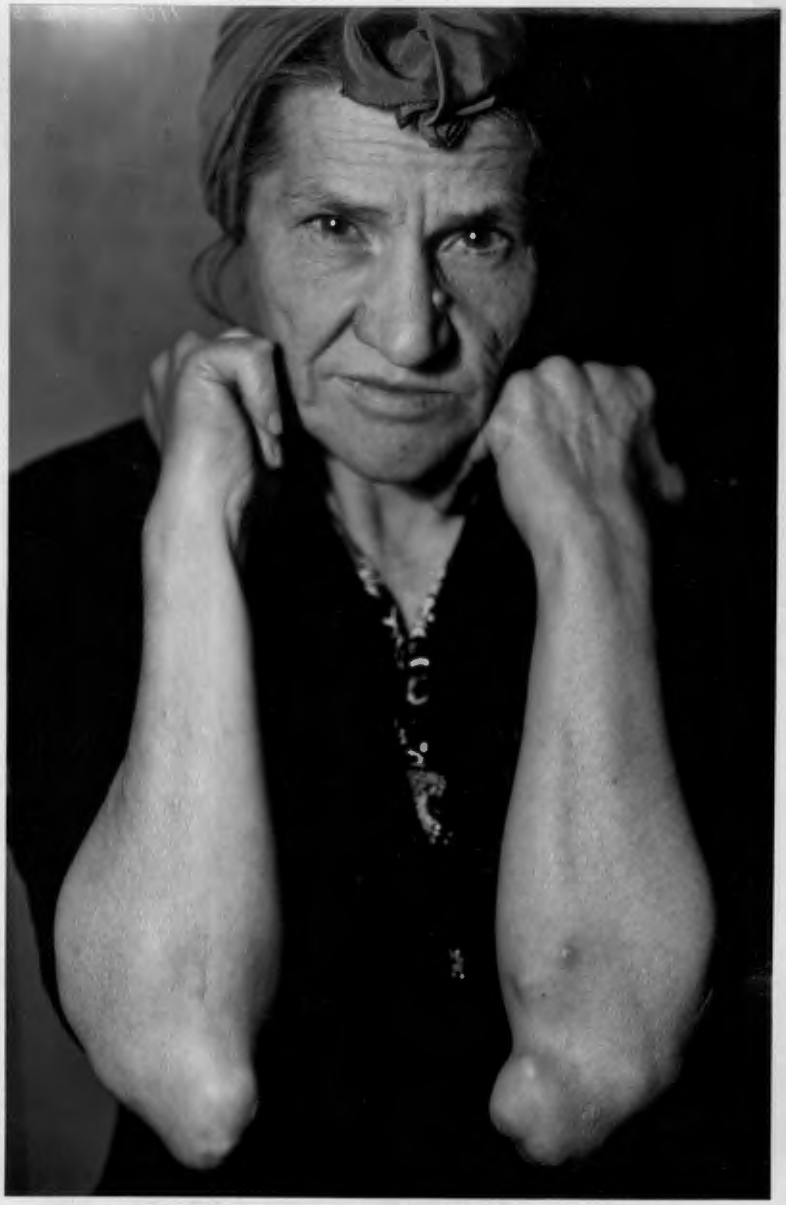
FIG. 72.

Case 26 : Rheumatoid Arthritis.

Symmetrical distribution of nodules over olecranon processes and ulnar border of forearms. (Compare with Fig. 74).

FIG. 73.

Subcutaneous Nodules.



Case 26 : Rheumatoid Arthritis.

Large symmetrical nodules over both olecranon processes and along left ulnar border. (Nodule on right ulnar border was removed - Fig. 72).

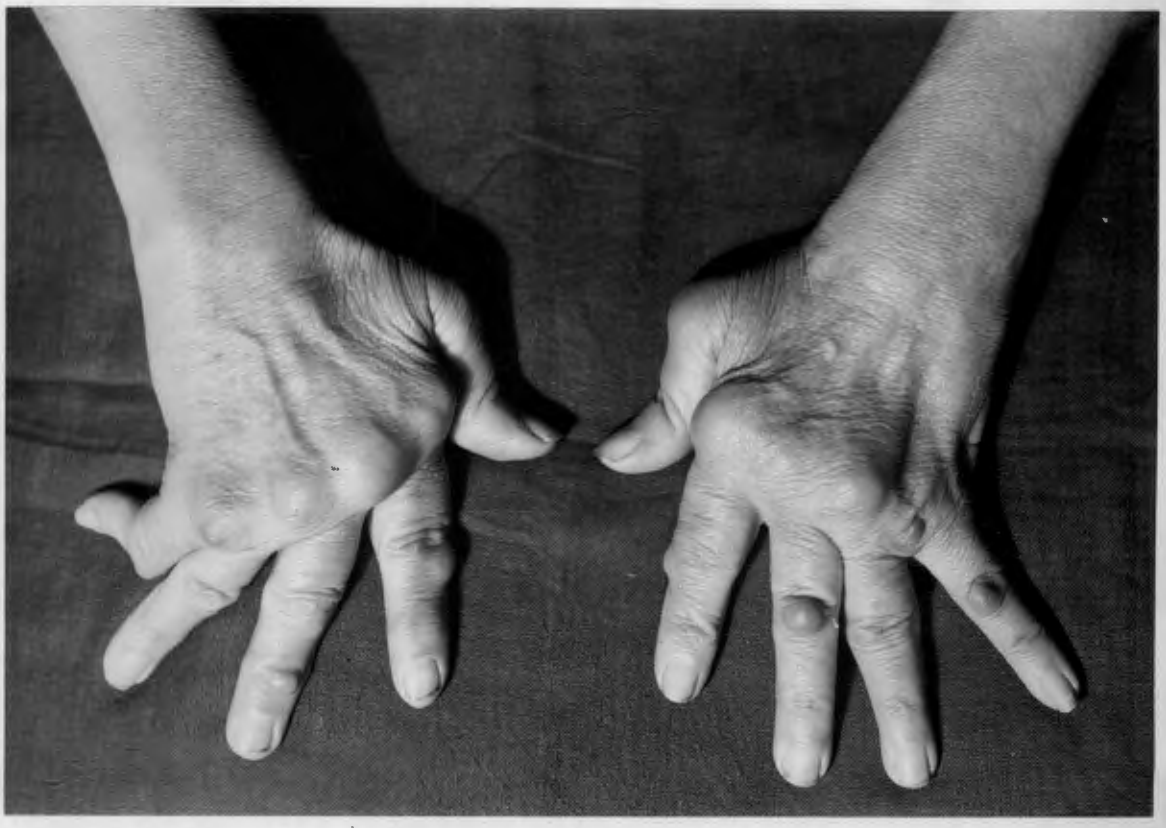
FIG. 74.

Xanthoma Tuberosum et Planum.

Case 89: Yellow xanthomata situated over olecranon processes in the skin and in the extensor digitorum tendon of the left index finger. Often symmetrically situated.

FIG. 75.

Subcutaneous Nodules.

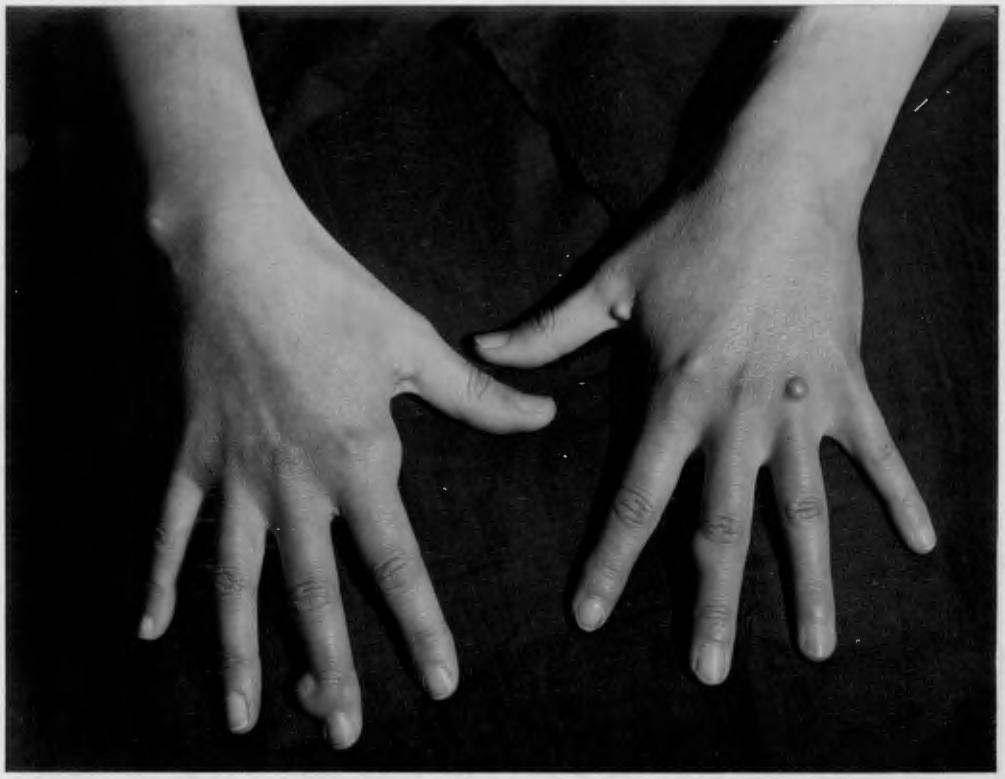


Case 26 : Rheumatoid Arthritis.

Multiple subcutaneous nodules on dorsum of hands distributed mainly symmetrically. (Compare with Fig. 76).

FIG. 76.

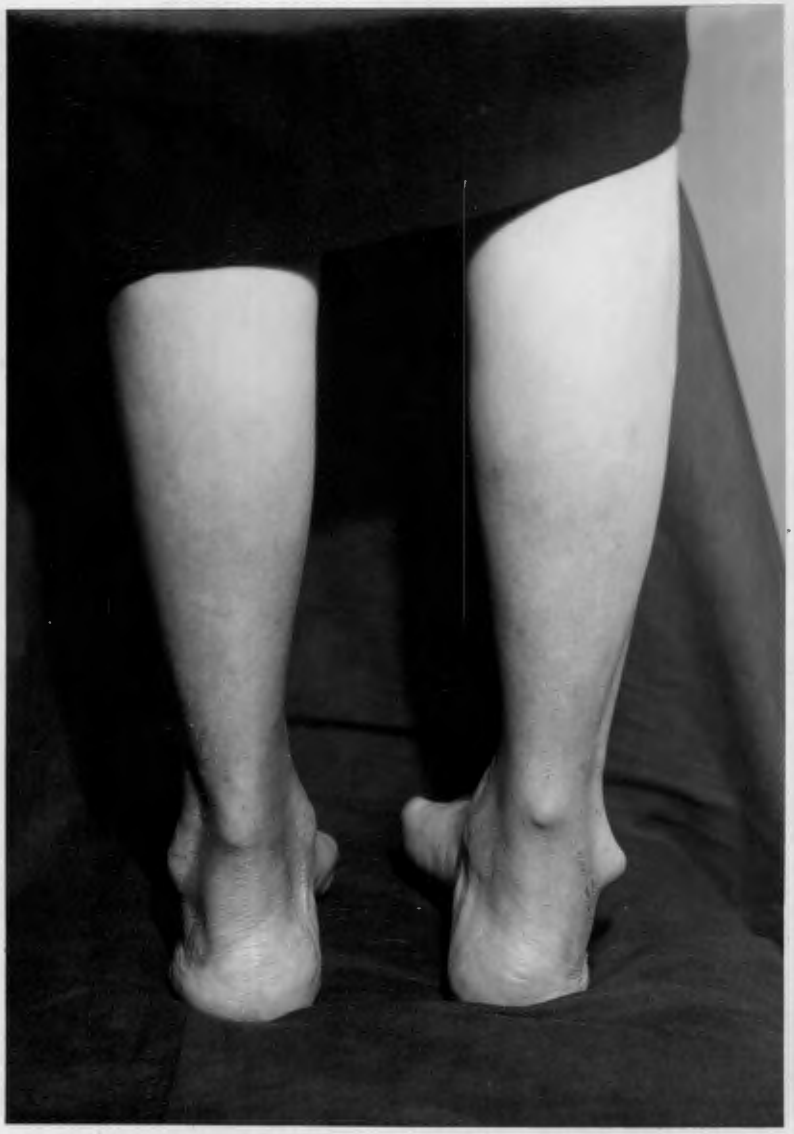
Xanthoma Tuberosum et Planum.



Case 89: Numerous xanthomata in skin and in tendons. (See Fig. 75).

FIG. 77.

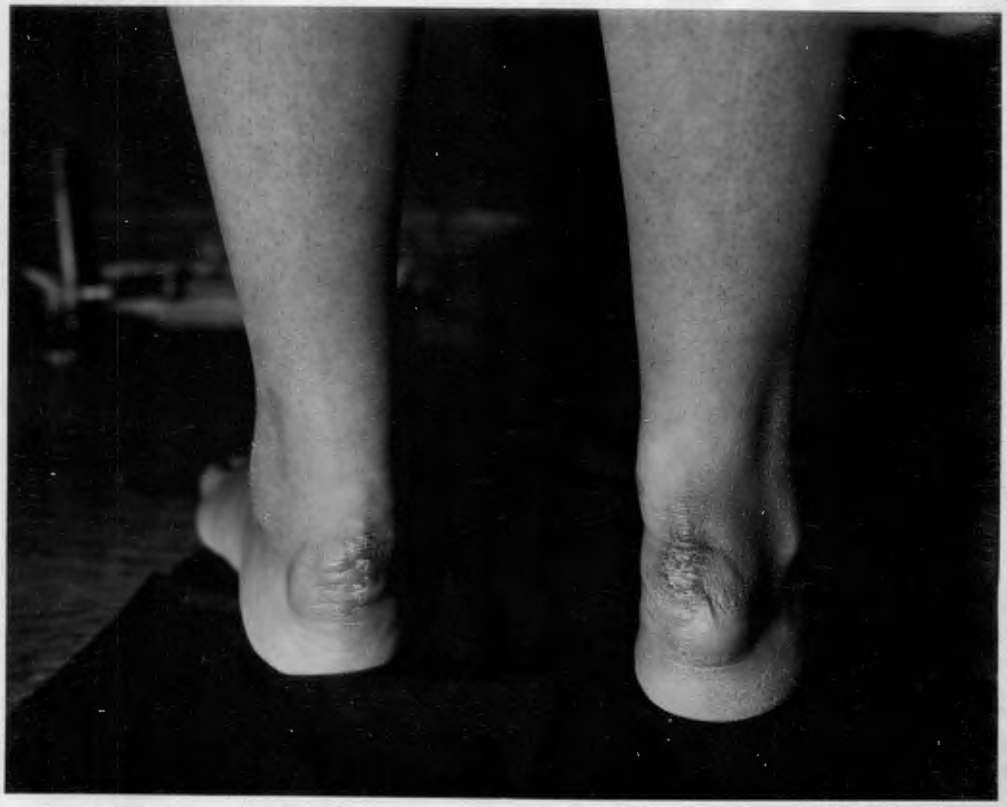
Subcutaneous Nodules.



Case 26 : Rheumatoid Arthritis.
Symmetrical nodules in tendon Achilles.
(Compare Figs. 78 and 79).

FIG. 78.

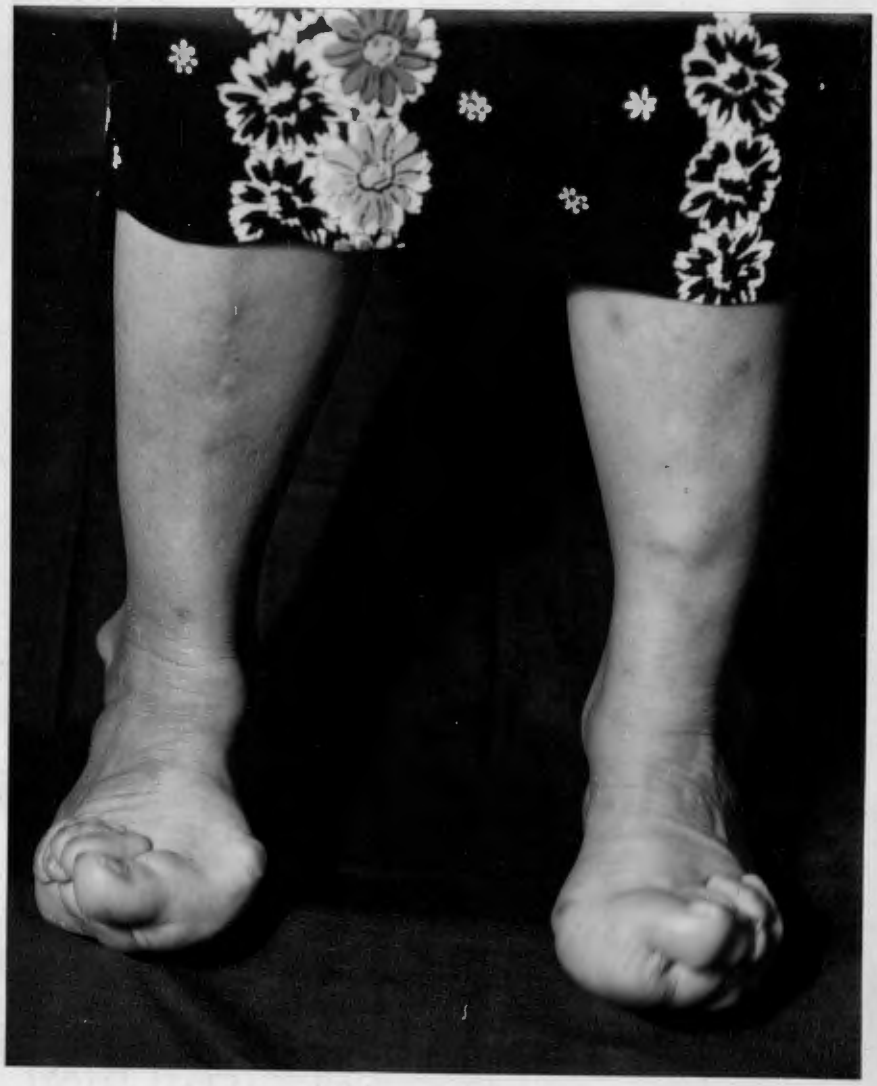
Xanthoma Tuberosum et Planum.



Case 89: Xanthomata of tendon Achilles. Scars are the result of previous attempts at removal.

FIG. 79.

Subcutaneous Nodules.

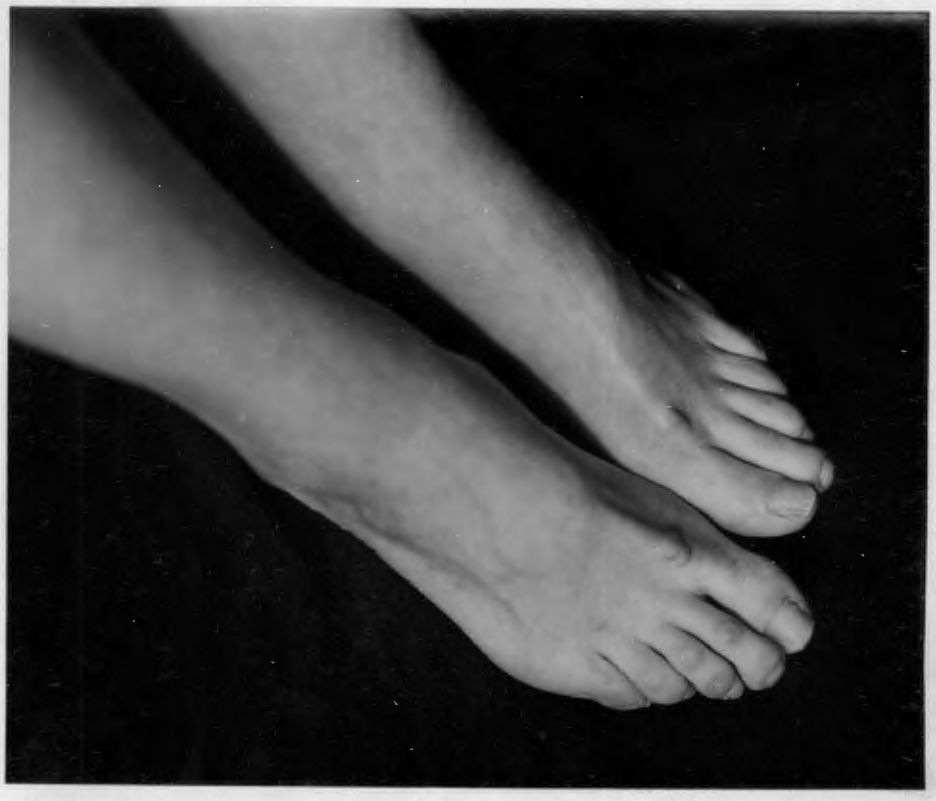


Case 26: Rheumatoid Arthritis.

Large subcutaneous nodule seen in muscles and tendons in anterior compartment of left lower leg, 3" superior to ankle joint.

FIG. 80.

Xanthoma Tubersum et Planum.



Case 89: Xanthomata in extensor hallucis longis tendons. Symmetrical involvement.

WEBER (1948) noted the occurrence of a subcutaneous nodule "near the elbow" in a case of granuloma annulare" with a histological appearance identical to that seen in rheumatoid arthritis nodules. This observation strongly suggests that the microscopical appearances of the nodules in rheumatoid arthritis cannot be regarded as absolutely pathognomonic. MORGAN and COMROE (1946) described the characteristic juxta-articular subcutaneous nodules in yaws. HENCH and ROSENBERG (1944) described transitory pararthritic swellings in some cases of palindromic rheumatism.

Other subcutaneous nodules from which rheumatoid arthritis nodules may have to be distinguished are the following: benign neoplasms (e.g. lipomata); atypical deposits of amyloid; pretibial myxoedema; neurofibromatosis, Christian-Weber's disease; Heberden's Nodes; calcinosis; Boeck's Sarcoidosis, etc.

SECTION IV.

THE CARDIAC LESIONS OF RHEUMATOID ARTHRITIS.

A. REVIEW OF THE LITERATURE.

Cardiac involvement in rheumatoid arthritis had been noted by investigators many years ago, but it was due mainly to the careful autopsy investigations of BAGGENSTOSS and ROSENBERG (1941a,1941b) that definite data was provided which awakened keen interest in the subject.

GARROD (1890) stated that "as a rule the heart is not injured in rheumatoid arthritis", and "that if patients with rheumatoid arthritis have valvular insufficiency one can assume a previous attack of rheumatic fever as the cause of the lesion". Most of these earlier reports on the subject are not of great value as one cannot be absolutely certain that the cases described correspond to those which today would be designated as "chronic rheumatoid arthritis". It seems very probable, after perusing the reports, that cases of osteo-arthritis (hypertrophic arthritis) and various types of infective arthritis were included in some series of cases as the types of chronic arthritis were seldom carefully defined.

1. PATHOLOGICAL FEATURES.

STILL (1897) reported the cardiac findings at the autopsies on 3 fatal cases of rheumatoid arthritis in children. In each case "adherent pericardium" was noted. These findings do not constitute proof of the presence of rheumatic heart disease as pericardial adhesions may be noted, in varying degrees, in routine autopsies, but they were suggestive as the pericardium was described as being "universally adherent" in each case. There was no sign of endocarditis in 2 of these cases but "the mitral valve was perhaps a little thickened" in the third case. His report does not include histological examination of the valves.

COLVER (1937) also described cardiac changes in 4 autopsies on cases of childhood rheumatoid arthritis. He noted "extreme pericardial adhesions" in 1 case and "moderate pericardial adhesions" in another case. None of the cases had rheumatic valvular lesions.

BAGGENSTOSS and ROSENBERG (1941a, 1941b) contributed a very valuable paper on the study of the cardiac lesions associated with chronic rheumatoid arthritis. Their studies were based on a careful examination of the lesions present in the heart at autopsies on

individuals...../

individuals suffering from the disease. The paper had the great advantage of being based on an objective analysis of autopsy material. There was no possibility that the results were influenced by selection of cases as every instance of rheumatoid arthritis which came to autopsy at the Mayo Clinic was included if adequate records of the nature of the joint disease were available. The criteria for the clinical and radiological diagnosis of their cases are clearly stated, and the authors make it plain that their cases were true examples of chronic, progressive, deforming polyarticular rheumatoid arthritis.

25 cases were studied and the duration of the arthritis varied from "months" to "years". Cardiac lesions were demonstrated in 14 cases which were indistinguishable from those produced by rheumatic fever. The authors give full details in regard to the degrees of mitral stenosis encountered, the incidence of dilatation of the left auricle, etc., and leave one in no doubt that they are handling cases of chronic rheumatic valvular disease.

The lesions were recognisable from the gross naked eye appearances in 13 cases. In these 13 cases

and in...../

and in the fourteenth case there was histological evidence of the presence of rheumatic lesions in the heart. They described the microscopical changes as being subacute lesions in some cases, chronic and active lesions in other cases, and inactive lesions in a few cases. They emphasized the important point that the rheumatic lesions were macroscopic and easily identified in almost every case.

They analysed the distribution of the rheumatic lesions. The mitral valve was the only valve affected in 5 cases; the mitral and aortic valves were affected in 3 cases; and the mitral, aortic and tricuspid valves were affected in 2 cases. This distribution corresponds, more or less, with our customary findings in cases of chronic rheumatic heart disease. The pericardium was involved in 2 of these cases with valvular lesions and in 3 cases "it was the only structure that revealed gross evidence of injury". It is interesting to note that the rather high incidence of possibly rheumatic pericardial lesions which appeared in the earlier reports by STILL (1897) and by COLVER (1937) is repeated in the more recent investigations.

In a...../

In a later paper (1944) ROSENBERG, BAGGENSTOSS and HENCH analyzed the cause of death in 30 cases of rheumatoid arthritis, representing all cases of the disease in which autopsies had been performed at the Mayo Clinic in the past 25 years. This series apparently included the 25 cases which BAGGENSTOSS and ROSENBERG described in 1941. "Cardiac lesions indistinguishable from those of rheumatic heart disease were found in 16 cases". Apparently 2 of the 5 autopsies performed since the earlier report revealed evidence of rheumatic heart disease. (BAGGENSTOSS and ROSENBERG, 1944).

SMYTH (1943) referred to 10 "unquestionable cases of rheumatoid arthritis" seen at Eloise, Michigan. He stated that "as far as could be determined, 50 per cent had both gross and microscopic lesions of rheumatic heart disease", but gave no further details about these cases.

Important additional contributions have been made by FINGERMAN and ANDRUS (1943), BAYLES (1943a, 1943b), and YOUNG and SCHWEDEL (1944). Their findings have confirmed those reported by BAGGENSTOSS and ROSENBERG (1941a, 1941b) and have clearly indicated the presence

of...../

of rheumatic heart disease in many of the autopsies on cases of rheumatoid arthritis.

FINGERMAN and ANDRUS (1943) analyzed 61 cases of rheumatoid arthritis obtained from the autopsy files of the Pathology Department, University of Minnesota, and of the local hospitals. Their cases of rheumatoid arthritis fulfilled certain criteria, viz. the cases were chronic and at least of several months duration; the disease involved at least 2 joints; and the cases showed some deformity of the joints or of their adjacent structures. They emphasised that they were discussing the "severe deforming advanced form of rheumatoid arthritis in which there are contractures, ankyloses, and atrophy of the extremities".

19 of the 61 cases (i.e.31 per cent) had "fibrous adhesive pericarditis; aortic, mitral or tricuspid valvular involvement; and combinations thereof of a rheumatic nature". Most of the lesions were old healed valve defects of varying degrees of deformity with thickening and retraction of leaflets, thickening and shortening of chordae tendinae, and fusion of some commissures. The mitral valve was affected in 16 cases and the aortic valve in 11 cases.

(2 of...../

(2 of the aortic valvular lesions were of the calcified nodular type). There was a fibrous adhesive pericarditis in 7 cases. Their analysis appears to be based mainly on anatomical observations and there was little mention of the microscopical appearances, but the descriptions of the valvular lesions correspond with those seen in chronic rheumatic valvular heart disease.

BAYLES (1943a,1943b) reviewed the 23 autopsied cases of rheumatoid arthritis encountered at the Robert Breck Brigham Hospital since 1914. His study appears to be very careful and meticulous. His criteria for the diagnosis of rheumatoid arthritis and of rheumatic heart disease are clear and acceptable. 6 of the 23 cases had anatomical changes in the heart valve leaflets similar to those that usually follow rheumatic fever. 4 of the cases affected had varying degrees of mitral stenosis; one had aortic stenosis; and one had "slight mitral stenosis" and "moderate" aortic stenosis. One of these 6 cases with valvular involvement had an "active adherent pericarditis obliterating the pericardial space", and another of these 6 cases had "a healed adjacent patch of pericarditis". Apart from these 6 cases 2

other...../

other cases had "adhesive non-constricting pericarditis" which had "produced cardiac hypertrophy in one case". Microscopically there was evidence of "activity" in only one case of the series with valvular involvement - a case of acute pericarditis which may have been due to active rheumatic fever (but which may have been due to the pulmonary tuberculosis and terminal bronchopneumonia which were present in the case).

In this series of 23 cases there were 5 examples of Marie-Strumpell's Ankylosing Spondylitis and they had about the same incidence of cardiac changes as the cases of rheumatoid arthritis of the usual type.

Subacute bacterial endocarditis was superimposed in 2 of the 6 cases on inactive rheumatic endocardial changes.

YOUNG and SCHWEDEL (1944) described the postmortem findings in 38 cases of rheumatoid arthritis in adults. The cases were closely followed in hospital in the "pavilion for the disabled" for periods varying from months to very many years before death occurred. They thus appear to comprise the most disabling, bedridden examples of the disease. They reported an extremely high incidence of rheumatic heart disease in their series, viz. 33 of the 38 cases had cardiac lesions which were

not ...../

not the result of arteriosclerosis nor of hypertension". 24 of the 33 cases had rheumatic valvular disease and one case had acute rheumatic pericarditis. They concluded that 25 of the 38 cases had "definite rheumatic heart disease". There were 2 cases of non-specific acute pericarditis and 6 cases of adherent or obliterative pericarditis without valvular lesions, and they have not included them in the 25 cases of "definite rheumatic heart disease". Of the 24 cases with rheumatic valvular disease there were 3 cases with acute rheumatic pericarditis and 7 cases of focal adhesive pericarditis or "milk spots". As "milk spots" have little, if any, pathological significance the authors have wisely not included cases showing only "milk spots" in their series of cases with "definite rheumatic heart disease".

Aschoff bodies were found in the myocardium in only one case; it is well-known that these microscopic lesions may be very difficult to find in indubitable cases of chronic rheumatic heart disease.

There was nothing striking in the distribution of the valvular lesions. The mitral valve was affected alone in 6 cases; the aortic valve alone in 3 cases; the mitral and aortic valves in 9 cases; the mitral,

aortic ...../

aortic and tricuspid valves in 5 cases, and all 4 valves in one case.

One of YOUNG and SCHWEDEL's cases (1944) showed certain interesting features. It was a case of rheumatoid arthritis with Marie-Strumpell's Ankylosing Spondylitis and with advanced mitral stenosis. This case strikingly illustrates the relationship which exists between these 3 diseases.

ROGEN (1947) investigated a series of rheumatoid arthritis cases clinically. Only one patient in the series came to autopsy and there was no macroscopical or histological evidence of rheumatic heart disease.

CLARK and BAUER (1948) have given a preliminary report on the cardiac abnormalities encountered in a group of 45 patients with definite rheumatoid arthritis in whom autopsies had been performed. Their report is very brief and they merely indicated that "pericarditis was found in 44 per cent and that "20 per cent had some degree of valvulitis which resulted in mitral stenosis in 14 cases". "A peculiar aortitis and aortic valvulitis with pannus formation was observed in one heart".

RAVEN, WEBER and PRICE (1948) have recently

described...../

described a very interesting and most unusual case of chronic rheumatoid arthritis which came to autopsy. Clinically the patient, a woman aged 62, had multiple subcutaneous nodules on her hands and elbows. Autopsy revealed the presence of identical nodules in the pericardium and endocardium which were visible macroscopically and had the characteristic histological appearances seen in the subcutaneous nodules. Nodules were also found in the larynx, lungs and pleurae. Their account is fully illustrated and clearly indicates this very unusual type of cardiac involvement in rheumatoid arthritis. CLARK and BAUER (1948) also noted that in 2 hearts in their series there were "nodules indistinguishable from the subcutaneous nodules of rheumatoid arthritis" but they do not indicate whether they were detectable with the naked eye or only on histological examination. The case described by RAVEN, WEBER and PRICE (1948) had a "moderate degree of mitral stenosis" and "some dilatation of the left auricle".

It is noteworthy that nearly all the postmortem examinations reported on cases of rheumatoid arthritis since the appearance of BAGGENSTOSS and ROSENBERG's papers (1941a, (1941b) have tended to confirm the fairly

high...../

high incidence of rheumatic heart disease. However, there have been exceptions. BENNETT (1943) compared the pathology of rheumatic fever and rheumatoid arthritis. He discussed the autopsy findings in 48 cases of rheumatoid arthritis and, with the exception of 3 cases of "myocarditis and aortitis of unknown etiology", he apparently noted no instances of rheumatic heart disease.

It is interesting to note the approximate average incidence of rheumatic valvular lesions in cases of rheumatoid arthritis. For this purpose the cases of BAGGENSTOSS and ROSENBERG (1941b), FINGERMAN and ANDRUS (1943), BAYLES (1943b) and YOUNG and SCHWEDEL (1944) have been selected as they comprise the most accurately reported series. The combined series of cases totals 147. Of this number approximately 59 cases had indubitable rheumatic valvular disease; cases of acute pericarditis and of pericardial adhesions without valvular lesions have not been included in this number. The conclusion reached from a review of the literature is that there is rheumatic valvular disease, at autopsy, in approximately 40 per cent of cases of chronic rheumatoid arthritis.

There...../

There is no close relationship between the duration of the rheumatoid arthritis and the incidence of rheumatic heart disease at autopsy. From an analysis of BAGGENSTOSS and ROSENBERG'S cases (1941b) it is obvious that the cases with proved cardiac lesions had been suffering from the arthritis for periods varying between 6 months and 23 years. Similarly there were cases of arthritis of long duration, e.g. one case of 30 years duration, which had no sign of rheumatic heart disease at autopsy.

BAGGENSTOSS and ROSENBERG (1941b), BAYLES (1943b) and YOUNG and SCHWEDEL (1944) have analyzed their cases to determine whether or not there was a higher incidence of rheumatic heart disease in those cases of rheumatoid arthritis which were acute in onset, and in those cases which had a past history of rheumatic fever. Their conclusions were similar: there was no greater liability to the development of rheumatic heart disease in cases which had an acute onset or in cases with a past history suggestive of rheumatic fever.

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HALL and ANDERSON (1943) claimed to have demonstrated minimal evidence of rheumatic heart disease microscopically, i.e. "rheumatic stigmas", in about 90 per cent of hearts which are usually considered macroscopically non-rheumatic. Whether this opinion is correct or not, the importance of the described incidence of rheumatic heart disease in rheumatoid arthritis is not altered, as the vast majority of the cases described by BAGGENSTOSS and ROSENBERG (1941b), and by the later investigators, had lesions easily recognizable macroscopically.

Severity of the Cardiac Lesions in Rheumatoid Arthritis.

BAGGENSTOSS and ROSENBERG (1941b) stated that the cardiac lesions encountered in rheumatoid arthritis were not as severe nor as widespread as such lesions are in the hearts of young people who have had rheumatic fever. They suggested that the comparative mildness of the cardiac damage may have been due to the fact that the age of onset of rheumatoid arthritis is, as a rule, later than the onset of rheumatic fever. It is generally believed, for example, that the heart in young children with rheumatic fever is more likely to be involved than in adults with rheumatic fever. COMROE (1944) also suggested that the later age of onset of rheumatoid arthritis, as compared with rheumatic fever, may explain

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the lack of severity of the cardiac lesions. However, YOUNG and SCHWEDEL (1944) found no essential difference, quantitatively and qualitatively, between the severity and extent of the cardiac lesions in rheumatoid arthritis and those associated with rheumatic fever. ROSENBERG has apparently altered his original views stated in 1941, as he subsequently reported (1947) that he had found "advanced lesions with tight mitral stenosis" in some cases, and that he was impressed "that these patients have advanced rheumatic cardiac lesions at post-mortem."

Relationship of Cardiac Lesions to Rheumatic Fever:

There appears to be no doubt that there is a high incidence of rheumatic cardiac lesions in cases of rheumatoid arthritis at autopsy. BAYLES (1941a) discussed the various possibilities to explain this finding. He indicated 3 possibilities:-

(i) that the finding of the rheumatic heart lesions is a coincidence. This suggestion appears untenable on account of the high incidence in several series of cases.

(ii) that the heart disease is in some way specially related to rheumatoid arthritis. The difficulty is that there are no essential differences

between...../

between these lesions and those seen after rheumatic fever; and

(iii) that there is a relationship between rheumatic fever and rheumatoid arthritis. This appears to be the best explanation. The concept is thus that while rheumatic fever and rheumatoid arthritis are quite distinct from each other in the majority of cases, there are cases - such as those of rheumatoid arthritis with cardiac lesions - which indicate the close relationship between these 2 diseases.

2. CLINICAL FEATURES:

The cardiovascular system has been investigated in chronic rheumatoid arthritis under 2 circumstances:

(i) Several workers have noted, or have obtained from past records, the clinical cardiological features of the cases before they came to autopsy. This group would supply information of great value as eventually the observer has anatomicopathological proof of the incidence of rheumatic heart disease in the cases examined clinically. Unfortunately few of the published papers adequately cover both clinical and autopsy observations, and where clinical features are included they have often been taken from records and files compiled by various persons other than by the writer who recorded the postmortem findings.

(ii) Other observers have investigated the cardiovascular system of a group of cases as out-patients, or as in-patients, and have perhaps seen one or two autopsies on their few fatal cases. This procedure thus lacks pathological confirmation or refutation of the features noted clinically, but it has the advantage that comparatively larger groups of cases can be examined

by...../

by various observers. As there is a striking discrepancy in most of the published reports between the clinical and the autopsy evidences of rheumatic heart disease it is still necessary for further clinical investigations to be made to aid in the elucidation of the problem.

STILL (1897) detected no evidence of valvular disease clinically in the 12 cases of rheumatoid arthritis in children which he reported. He noted "physical signs suggestive of adherent pericardium" in 2 cases which did not come to autopsy.

BOAS and RIFKIN(1924) examined 80 cases of "Arthritis deformans" in the orthopedic wards of the Montefiore Hospital and paid special attention to the heart. They defined "arthritis deformans" (or "chronic multiple arthritis") as "the group of arthritis cases which have as a prominent feature a tendency to chronicity and to more or less permanent changes in joints or structures about joints". However, in tabulating the nature of the joint lesions they included 54 cases of "atrophic arthritis", so it is obvious that they included osteo-arthritis in their series of "arthritis deformans". They noted "valvular disease, the result of endocarditis"

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in 17.5 per cent of the 80 cases examined. The criterion for their diagnosis of "valvular disease on an infectious basis" was the presence of a diastolic murmur, or of an apical systolic murmur with cardiac enlargement in the absence of arteriosclerosis, hypertension or other causes of "mitral insufficiency". They are thus tacitly assuming that the presence of an apical systolic murmur with cardiac enlargement, in the absence of an obvious cause, always indicates chronic rheumatic valvular disease. Their investigations are therefore of very little value as the criteria for the diagnosis of both rheumatoid arthritis and rheumatic heart disease are unacceptable.

DAWSON and TYSON (1935) reported that 7 in a series of 100 consecutive cases of "classical rheumatoid arthritis" had "unequivocal signs of rheumatic heart involvement". He brought forward some evidence to suggest that the onset of all these cases with recognisable cardiac involvement occurred in the earlier decades of life, between the ages of 15 and 25 in the majority of instances.

YOUNG and MACMAHON(1935) undertook an investigation to determine whether or not certain cases of rheumatic fever may develop the same chronic joint lesions as are

usually...../

usually seen in rheumatoid arthritis. They described 10 cases which at their onset resembled "acute rheumatic polyarthritis" but which subsequently developed chronic atrophic changes in the joints. The duration of the chronic arthritis varied between 6 months and 21 years at the time of examination. 9 of the 10 cases had clinical evidence of mitral stenosis and the tenth had "cardiac enlargement". It is not clear, on reading the case reports, to determine whether the cases commenced as rheumatic fever and then developed chronic arthritis, or whether they were cases of rheumatoid arthritis with an acute onset. This difficulty is one which is a well known problem in clinical medicine, and it may be that the 2 conditions are not really so very dissimilar.

The article is useful as it indicates the clinical association between rheumatic heart disease and chronic rheumatoid arthritis. The criticism of the paper is that the authors have apparently specially looked out for such cases, and their results are therefore not a true reflection of the incidence of the combination of the two conditions.

COLVER (1937) was unable "to demonstrate a valvular lesion"...../

lesion" in his series of rheumatoid arthritis cases in childhood, even though "the possibility of cardiac complications was considered". MASTER, JAFFE and DACK (193) described a case of chronic rheumatoid arthritis with well established mitral stenosis and aortic regurgitation which developed acute pericarditis. There are other reports of similar isolated cases in the literature but, beyond indicating the association, they are little value in determining the general incidence of clinical cardiovascular involvement in chronic rheumatoid arthritis.

BAGGENSTOSS and ROSENBERG (1941b) observed that in only 7 of their proved 14 cases of rheumatoid arthritis was there any clinical evidence of heart disease. The remaining cases were known to have had no clinical signs nor symptoms of heart disease. They noted that many patients with chronic rheumatoid arthritis have rheumatic cardiac lesions which do not "attract the attention of either patient or physician".

This problem of the discrepancy between the high pathological incidence and the low clinical incidence of rheumatic heart disease has interested other investigators, but it has remained unsolved. HENCH (1941a) stated...../

stated, in the discussion on BAGGENSTOSS and ROSENBERG'S paper (1941a), that his own past experience harmonised with other clinical analyses which found "inflammatory cardiac lesions rare in chronic atrophic arthritis." HENCH has brought forward the suggestion that the cardiac lesions may go unrecognised because of the severely restricted life led by chronic arthritics.

SMYTH (1943) also noted that the diagnosis of rheumatic heart disease was established in no instance during life in the 5 cases with gross autopsy evidence of cardiac lesions. BAYLES (1943b) stated that only 4 of his series of 23 cases had clinical signs of rheumatic heart disease antemortem, including 2 cases of subacute bacterial endocarditis superimposed on rheumatic heart disease. FINGERMAN and ANDRUS (1943) observed, from an analysis of the past clinical records of their autopsied cases, that only 7 of the cases with valve deformities had "characteristic murmurs". 6 of their 19 cases showed signs of congestive cardiac failure. YOUNG and SCHWEDEL (1944) stated that each of their cases had been frequently examined by many observers over a long period of hospitalisation. It appeared nevertheless that the

diagnosis...../

diagnosis of rheumatic heart disease had not been made clinically in 14 of the cases in their series (24 of which were later shown to have rheumatic valvular disease at autopsy). In YOUNG and SCHWEDEL'S cases cardiac symptoms were relatively unimportant or non-existent throughout the major part of their lives; they sought advice for their joints, not for their cardiac disease.

FRASER (1945) investigated the effect of cryotherapy in 110 patients with rheumatoid arthritis. He noted, as an incidental finding, that "valvular disease of the heart was present in 14 per cent of the patients", but gave no further details and did not state his criteria for the diagnosis of "valvular disease".

FEIRING (1945) discussed the changes in the cardiovascular system in 8 cases of rheumatoid arthritis. 2 of the cases had rheumatic valvular disease clinically, but the contribution is of limited value as it is not quite certain that they were true cases of chronic rheumatoid arthritis: in the first case, e.g. the duration of the attack of arthritis with which the patient presented appeared to have been only approximately one month.

GRANIRER...../

GRANIRER (1946) described a case of chronic rheumatoid arthritis which developed an acute pericarditis with effusion. The patient recovered after a month. During his stay in hospital he had a transitory attack of auricular fibrillation. The conclusion appears to be that the patient had exhibited the pericarditis as a manifestation of rheumatic heart disease.

ROGEN (1947) has added a useful contribution to the subject. He recorded the results of a detailed examination of the cardiovascular system in 33 consecutive cases of rheumatoid arthritis admitted to municipal hospitals in Glasgow. The rhythm was regular in all the cases. In spite of a "particularly careful search" there was no evidence of mitral stenosis in any of the cases. A faint systolic murmur, sharply localised, was heard at the apex in 8 cases; there was no associated loud sharp first sound nor an accentuated second sound at the pulmonic area. ROGEN considered these murmurs to be "functional in origin". In only one case was there a loud systolic murmur at the apex conducted into the axilla. It is evident, thus, that none of the 33 cases

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had any conclusive evidence of rheumatic valvular disease, and yet - according to autopsy statistics of other workers - it could be predicted that about 40 per cent have in fact got rheumatic valvular disease! These results indicate once again the extraordinary discrepancies between the pathological and clinical observations on the heart in rheumatoid arthritis.

ROSENBERG, BISHOP, WEINTRAUB and HENCH (1947) found that the incidence of rheumatic heart disease, judged on the basis of "bedside evidence" was not notably higher in a series of 147 cases of rheumatoid arthritis than in a control group of 100 normal individuals. CECIL (1947) contributed to the discussion on their paper by remarking that it was "amazing how little trouble the average rheumatoid arthritis patient has with his heart". The incidence of rheumatic heart disease noted in the above series of 147 cases was subsequently stated by ROSENBERG (1948) to be approximately 3 per cent - about the same incidence as in the control series. CLARK and BAUER (1948) briefly reported the findings in a group of 45 patients with rheumatoid arthritis on whom autopsies had been performed: mitral stenosis was present at postmortem in 14 cases but had

been...../

been apparently demonstrable clinically in only 5 instances.

FLETCHER (1947) described cases which illustrated the difficulties in differentiating rheumatic fever and rheumatoid arthritis. He described several cases which developed rheumatoid arthritis and which had shown, at some time or other, features indicative of cardiac involvement of the type normally seen in rheumatic fever. His cases serve to illustrate once again the relationship which may exist between the 2 diseases.

BUCCHESI and BUCCHESI (1947) found no clinical signs of heart disease "as a direct, indirect, or remote consequence of the arthritis" in 55 cases of rheumatoid arthritis with subcutaneous nodules.

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Several of the cases of rheumatic heart disease and rheumatoid arthritis have shown signs of cardiac failure before they died. 2 of the 6 cases described by BAYLES (1943b) died with congestive cardiac failure, and 22 of YOUNG and SCHWEDEL'S series of 33 cases (1944) (including those with valvular lesions and those with pericardial lesions at autopsy) had signs of congestive cardiac failure. YOUNG and SCHWEDEL (1944) expressed

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the opinion that it was quite apparent that the cardiac lesions played a comparatively minor role in the clinical picture except as a late manifestation and also as a mode of death.

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HENCH (1947) has aptly summarized the present position of the problem by remarking that "the hearts of most living rheumatoid arthritis patients appear to be quite normal as far as current clinical methods of examination permit one to determine, even though the hearts of most dead rheumatoid arthritis patients reveal disease". ROSENBERG (1948) considered that the developments since his original findings in 1941 have been "most puzzling". He remarked that he had noted a recent tendency on the part of some cardiologists to teach that patients with rheumatoid arthritis often develop serious rheumatic heart disease, and considers that "this may be the case, but we are not yet certain". He concluded that the problem needs much more study.

3. ELECTROCARDIOGRAPHIC FEATURES.

There is scanty reference to electrocardiographic findings in rheumatoid arthritis in the literature. WHITE (1944) and KATZ (1946) mentioned the subject very briefly.

MASTER and JAFFE (1932, 1934) described the electrocardiograms recorded in 63 cases of rheumatic fever and in 50 cases of rheumatoid arthritis. They came to the conclusion that the vast majority of cases of rheumatic fever showed significant electrocardiographic abnormalities, whereas hardly any cases of rheumatoid arthritis showed significant abnormalities. They emphasised that the outstanding feature in their investigations was the lack of electrocardiographic evidence of myocardial damage in patients with rheumatoid arthritis. They performed daily electrocardiographic investigations on their patients from the day of admission to the day of discharge, so that the thoroughness of the investigations is beyond question.

Unfortunately there is a drawback to the value of their investigations. On reading their articles carefully it is quite obvious that none of their cases classified as "rheumatoid arthritis" were chronic cases. They were all

examples..../

examples of what they have designated "acute rheumatoid (infectious) arthritis". The average hospital stay of these cases was 53 days and all the cases recovered. The longest duration of any of the cases was 108 days. The conclusion one must reach is that they were performing electrocardiographic investigations on a mixed variety of cases of "acute rheumatoid (infectious) arthritis". It is possible, of course, that their series did include some cases of true acute rheumatoid arthritis of unknown etiology which recovered in 2 months, but many other types of acute arthritis may have been included as well. Their analyses, then, do not indicate the incidence of electrocardiographic abnormalities in cases of chronic rheumatoid arthritis with a duration of months or years.

YOUNG and SCHWEDEL (1944) have recorded the electrocardiographic changes noted in 16 of their 25 cases of rheumatoid arthritis with rheumatic heart disease proved at autopsy. They encountered a high incidence of abnormalities in these 16 cases, some of which were minor and others were more significant. Left axis deviation occurred in 11 cases - in 6 of these it was the sole abnormality; in 3 cases it was associated with auricular fibrillation; in one case it was associated with prolongation of the PR interval to .25 seconds and with

inversion...../

inversion of T1 and T2; and in one case it was associated with intraventricular block. Right axis deviation occurred in 3 cases - in one case it was the sole abnormality; in another case it was associated with ventricular extrasystoles; and in a third case it was associated with prolongation of the PR interval to .42 seconds and with intraventricular block. In 2 of the 16 cases the tracings were normal. There is no mention in the report on the remaining 9 cases; presumably no tracings were recorded in them.

These findings are very interesting as this was the only series of cases studied at autopsy in which the electrocardiographic features were recorded. They are also of importance as they indicated that significant abnormalities were encountered in a fairly large proportion of the cases.

FEIRING (1945) recorded the results of his electrocardiographic findings in 6 of his 8 cases. It has already been noted that it is difficult to be certain whether all his 8 cases were truly examples of rheumatoid arthritis or not. In any event electrocardiographic abnormalities were recorded in 5 cases; in the sixth case the tracings were normal. The abnormalities

encountered...../

encountered included bundle branch block; inversion of the T wave in leads 2, CF2 and CF4; left axis deviation with inversion of T2; and prolongation of the PR interval to .22 seconds.

GRANIRER (1946) described the electrocardiographic features of his case of chronic rheumatoid arthritis which developed pericardial effusion. The tracings initially showed elevation of the ST segment in leads 1 and 2, followed at a later date by flattening of the T wave in all 3 limb leads. At one period, too, transitory auricular fibrillation was noted.

ROSENBERG, BISHOP, WEINTRAUB and HENCH (1947) included electrocardiographic investigations in their examination of 147 cases of rheumatoid arthritis. The opportunity for making serial tracings only arose in one patient. They did not describe their results in detail but apparently they did not note any results of special value.

ROGEN (1947) recorded the electrocardiographic findings in 29 patients of his series of 33 consecutive cases. Left axis deviation occurred in 17 cases; "there was a considerable incidence of slurring of the QRS complexes"; and the T wave was inverted in one case

in...../

in lead One, in another case in lead 2, and in a third in lead CF4. No records showed abnormal ventricular preponderance; the P waves were normal; and the rhythm was unaffected. ROGEN considered that the abnormalities which he encountered were consistent with the coronary artery disease which was to be expected in the elderly people who formed the majority of his patients in the series.

LUCCHESI and LUCCHESI (1947) performed electrocardiographic investigations in 19 of their series of 55 cases. They used the 3 standard leads and chest leads CF1 and CF5. Abnormal notching of the QRS complex; bundle branch block, and flattening of T1 were found in 3 elderly cases with hypertension. Another 3 cases with Hypertension showed left axis deviation. There was thus no electrocardiographic evidence of rheumatic heart disease.

From the various reports it appears that a large number of electrocardiographic tracings have not been made in cases of chronic rheumatoid arthritis. When tracings have been recorded they have not usually shown a high incidence of significant abnormalities, with the exception of YOUNG and SCHWEDEL'S group of cases (1944).

LUCCHESI...../

4. RADIOLOGICAL FEATURES.

There is occasional mention of the radiological appearances of the heart in some of the reported series of cases of rheumatoid arthritis, but technical difficulties have prevented radiological investigations on a large scale.

FIELD (1941) published the report of a case "showing combined features" of acute rheumatic fever and rheumatoid arthritis. The X-Ray of the heart of the patient (a child aged 7 years) revealed "slight general enlargement with a tendency to pearshape". However, on analysing the clinical features of the case there appears to be no good reason for rejecting the diagnosis of rheumatic fever with some atypical features, and there seems no necessity for diagnosing rheumatoid arthritis at all.

FEIRING (1945) noted that the transverse diameter of one of his cases increased from 106 mm. to 123 mm., but he did not state the width of the greatest transverse diameter of the chest, and nor did he state whether the plates were taken in corresponding phases of respiration.

GRANIRER (1946) described the radiological appearances of his case of chronic rheumatoid arthritis in

which...../

which a pericardial effusion developed.

ROGEN (1947) performed radiological examinations in the earlier members of his series of 33 cases but soon found the procedure impracticable because of the technical difficulties associated with gross deformities of the joints and with the inability to get many patients into suitable positions.

RAVEN, WEBER and PRICE (1948) detected some cardiac enlargement radiologically in their case of rheumatoid arthritis which at autopsy was found to have a moderate degree of mitral stenosis and subcutaneous nodules in the pericardium and endocardium.

BAGGENSTOSS and ROSENBERG (1941b), BAYLES (1943b), and other investigators who have reported the autopsy findings do not include the results, if any, of radiological examinations performed during the patients' lifetimes.

ROSENBERG, BISHOP, WEINTRAUB and HENCH (1947) included radiographic examination of the cardiac contours in 147 patients with rheumatoid arthritis. They remarked that it was unfortunate that all the patients could not be fluoroscoped. They did not give a detailed report on their findings but there were apparently no results deserving of special comment.

LUCCHESI and LUCCHESI (1947) performed radiological examinations of the heart in 19 cases. 8 showed left ventricular enlargement due to hypertension; 11 showed no changes in the size of the heart.

B. RESULTS OF PRESENT INVESTIGATIONS.

The presence of valvular disease was detected with certainty in 4 of the 70 cases examined. The details of these 4 cases are as follows:

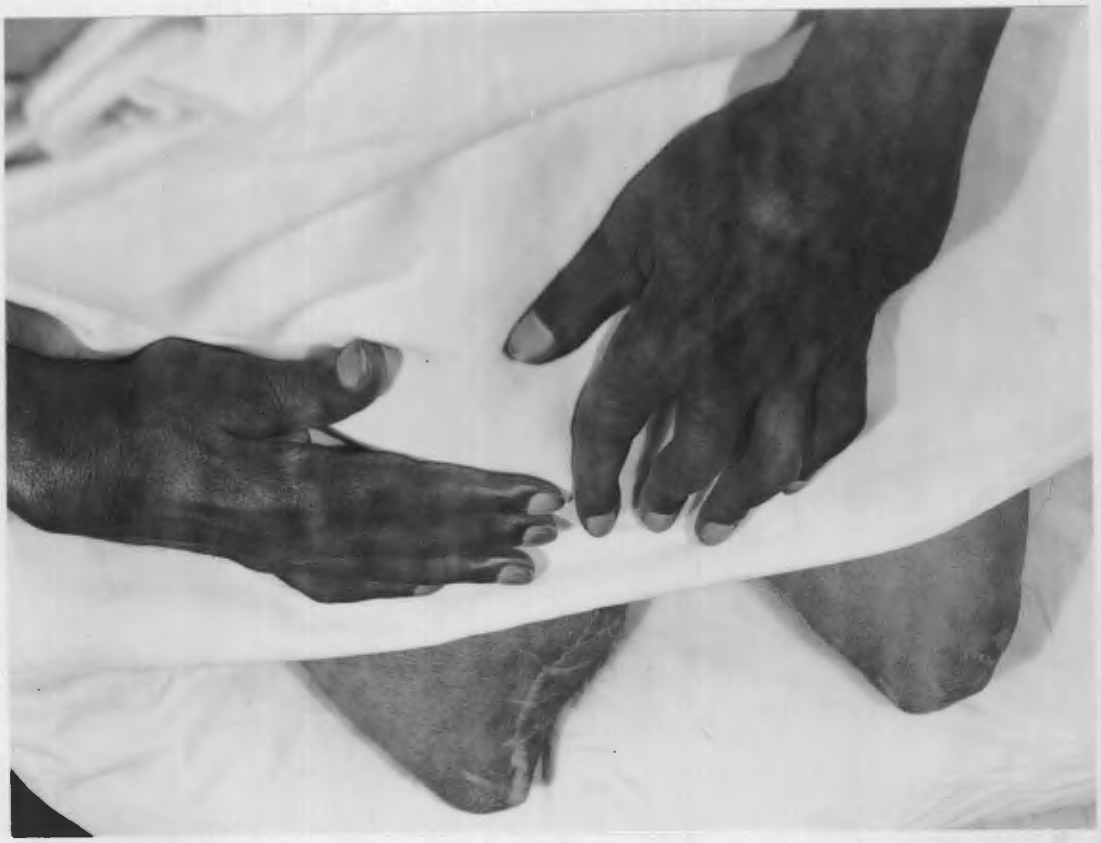
1. Case 2, a male aged 43, developed rheumatoid arthritis at the age of 20. The disease persisted for 16 years and then, according to the patients' history, "all the symptoms disappeared and he was quite well for one year". An attack of iritis occurred a few months after the onset of the arthritis at the age of 20. Six years ago there was a recurrence of the disease and it progressed causing contractures and ankylosis of many joints. The terminal interphalangeal joints were also involved. (Fig. 3). Onycholysis of the finger nails occurred at the same time as the recurrence of the polyarthritis. A few months after the recurrence of the arthritis both feet suddenly became gangrenous and the legs were amputated above the knees. (Fig. 81).

On examination a small subcutaneous nodule, about 0.5 cm. in diameter, was present over the left ulnar border, about 1½" distal to the tip of the olecranon process. (Fig. 82). Its histological appearances were described in Fig. 47 . There was cardiac enlargement clinically confirmed by radiological examination (Fig. 83). A loud systolic murmur and

a soft ...../

FIG. 81.

Bilateral Amputation of Legs.

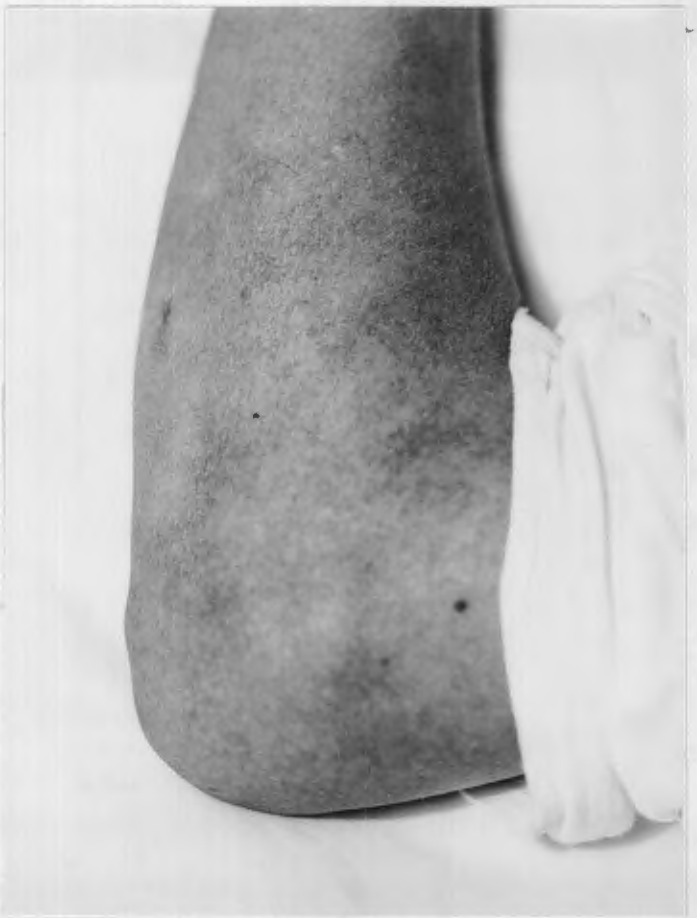


Case 2: Rheumatoid Arthritis.

Characteristic deformity of hands. Bony ankylosis of terminal interphalangeal joints. (See Fig. 3) Both legs amputated above the knees on account of gangrene of feet. Clinical and radiological evidence of aortic regurgitation (See Fig. 83).

FIG. 82.

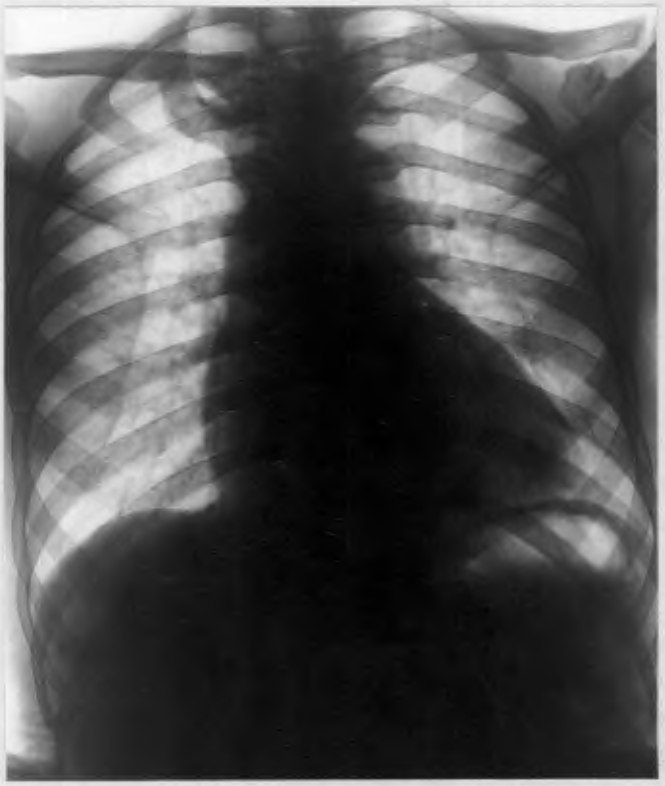
Subcutaneous Nodule in Rheumatoid Arthritis.



Case 2 : Rheumatoid Arthritis with Aortic Regurgitation.
Very small nodule detectable on ulnar border of left forearm. (See Fig. 47 for histology).
Fig. 83 illustrates the cardiac enlargement radiologically.

FIG. 81.

Postero - Anterior View of the Heart.



Case 2: Rheumatoid Arthritis with Aortic Regurgitation.

The heart is enlarged and the enlargement appears mainly due to left ventricular enlargement. The left border is somewhat straightened but there is no excessive prominence of the pulmonary conus. There was no left auricular enlargement in the right oblique view.

a soft blowing early diastolic murmur were audible at the aortic area. The diastolic murmur was propagated down the left side of the sternum to the apex but its character and timing remained unaltered; there was no evidence of mitral stenosis. The rhythm was regular and the blood pressure was 135/60 mm. Hg. The femoral pulses were palpable. The electrocardiogram showed depression of the ST segment and inversion of the T wave in Lead II. The phonocardiogram confirmed the presence of the systolic and diastolic murmurs. The blood Wasserman reaction was negative.

2. Case 33, a male, aged 21, was admitted with an acute "flitting" polyarthritis of 10 days' duration resembling rheumatic fever. On examination there was evidence of aortic regurgitation and mitral stenosis, as shown by the presence of a soft, blowing early diastolic murmur at the aortic area and a low-pitched "rumbling murmur" at the apex. The polyarthritis responded incompletely to full doses of salicylates and pain and swelling persisted in the fingers and wrists. The elbows and shoulders also remained painful. He was seen again one year later on account of progressive dyspnoea on exertion and a recent haemoptysis. The cardiac findings were unchanged and radiological examination confirmed the diagnosis of cardiac enlargement, aortic regurgitation and mitral stenosis. The rhythm was regular and the blood pressure was 112/56 mm. Hg. There was fusiform swelling

of ...../

of the proximal interphalangeal joints and of the wrists, wasting of the thenar and hypothenar eminences and ulnar deviation of the fingers.

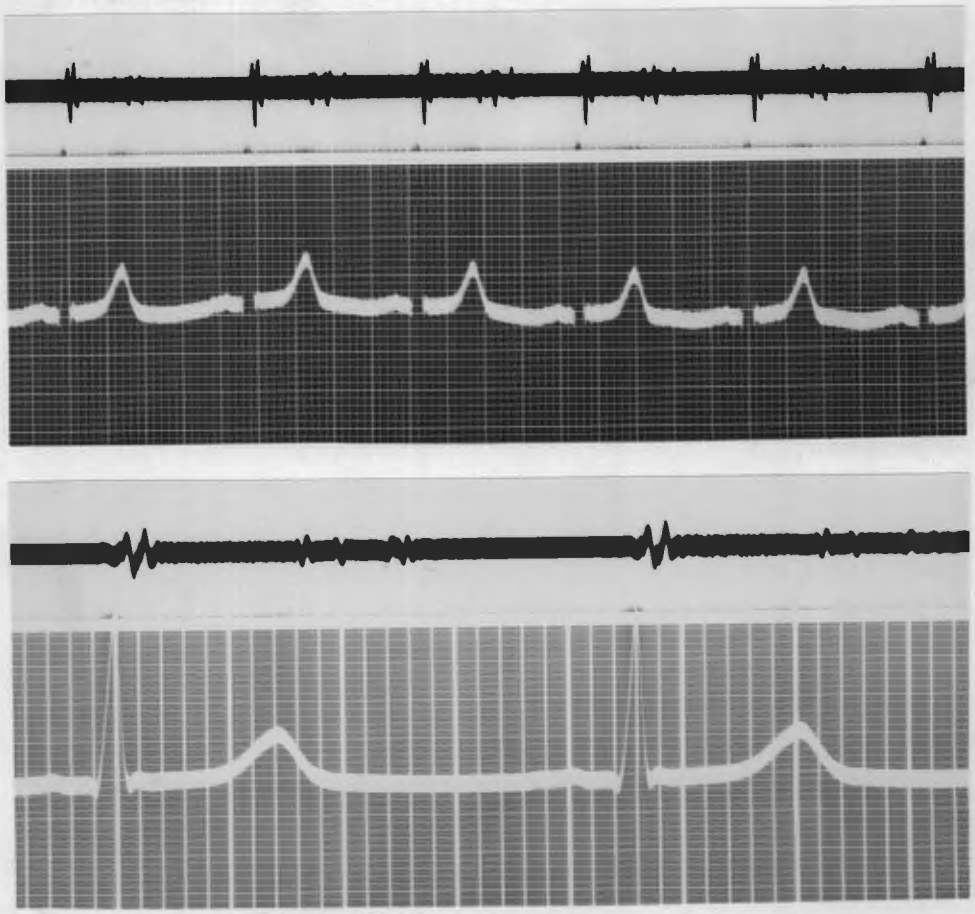
3. Case 43, a female, aged 17, had chronic polyarthritis of the knees, ankles, metacarpophalangeal and proximal interphalangeal joints for one year, which improved but did not subside after full doses of salicylate were given continuously for 2 months. The affected joints were all slightly painful and slightly swollen. "Carpal cysts" were present on the dorsum of both wrists. The pulse was regular and the blood pressure was 110/60 mm. Hg. There was cardiac enlargement and unquestionable evidence of both aortic regurgitation and mitral stenosis on clinical examination. This was confirmed radiologically. The phonocardiogram revealed the presence of a diastolic murmur at all areas (Fig. 84). There was slight notching of the P wave in all the limb leads of the electrocardiogram.

4. Case 52, a female, aged 46, had typical rheumatoid arthritis of approximately 5 years' duration. The clinical and radiological appearances of the affected joints were characteristic (Figs. 85 and 86). The patient was admitted with signs of congestive cardiac failure of several months' duration. The rhythm of the pulse was regular. There was unquestionable evidence of mitral stenosis on clinical examination, including the presence of a rumbling diastolic murmur and a diastolic thrill at

the...../

FIG. 84.

Phonocardiogram.

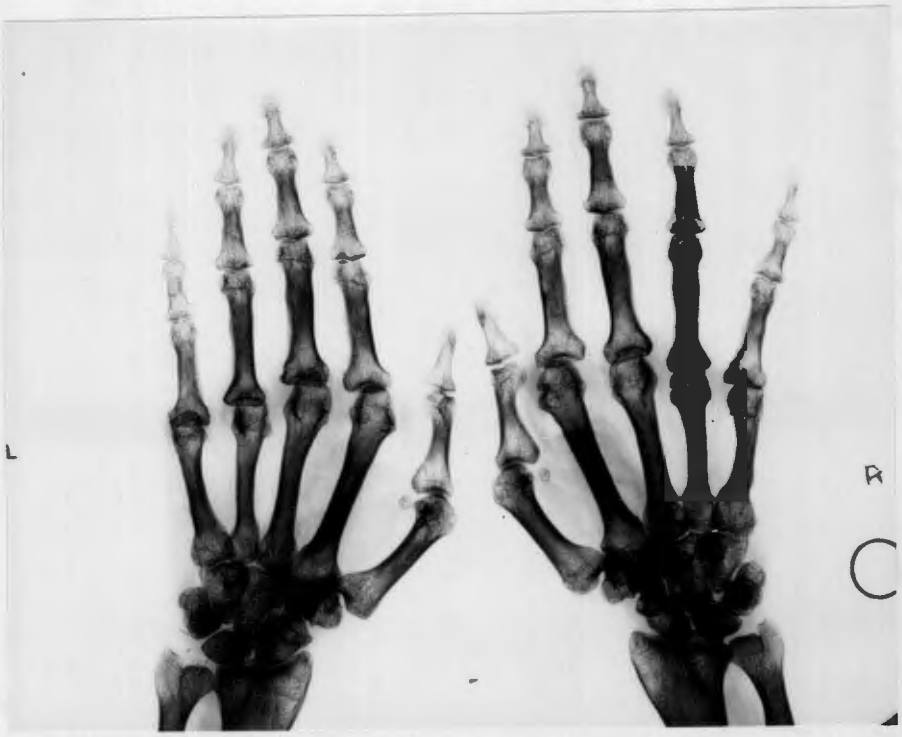


Case 43 : Rheumatoid Arthritis with Aortic Regurgitation and Mitral Stenosis.

The tracing was recorded at the apex. A mid-diastolic murmur is detectable.

FIG. 85.

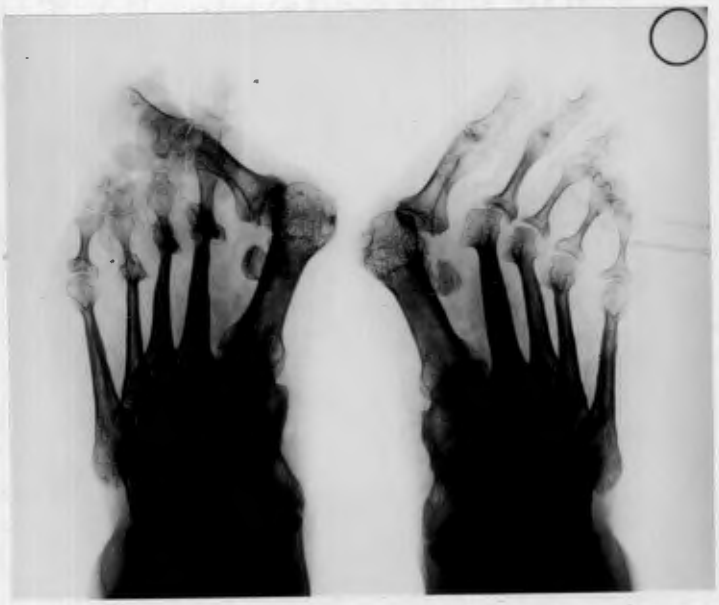
Radiological Changes in Hands.



Case 52: Rheumatoid Arthritis with Rheumatic Heart Disease.
Radiological changes minimal. Slight narrowing of joint spaces of proximal interphalangeal joints and osteoporosis of the ends of the phalanges. (See Figs. 86, 87 and 88 for radiological changes in feet and in heart).

FIG. 86.

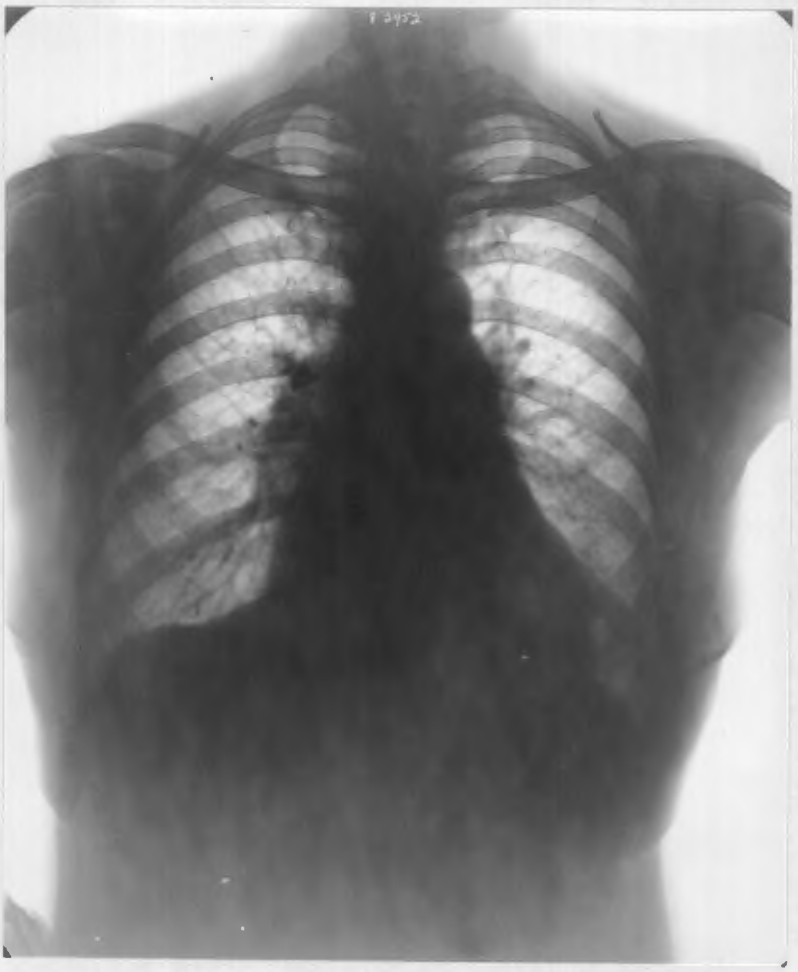
Radiological Changes in Feet.



Case 52: Rheumatoid Arthritis with Rheumatic Heart Disease.
Characteristic eversion deformity of the toes.
Osteoporosis and atrophy of the phalanges.
Clinical and radiological features of mitral stenosis (See Fig. 87, 88.)

FIG. 87.

Postero-Anterior View of the H e a r t.

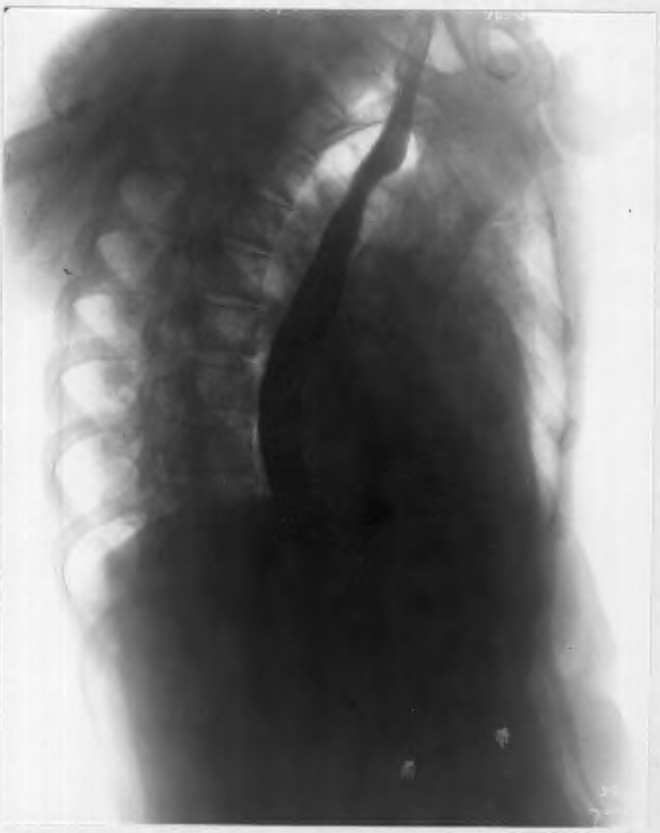


Case 52: Rheumatoid Arthritis with Mitral Stenosis.

Marked prominence of the pulmonary conus.
(See Fig. 88 for right oblique view).

FIG. 88.

Right Oblique View of the Heart.



Case 52: Rheumatoid Arthritis with Mitral Stenosis.

Considerable enlargement of the left auricle indenting the barium-filled oesophagus.

the apex. The radiological examinations of the heart confirmed the presence of mitral stenosis (Fig. 86 and Fig. 87).

.. ..

In addition to those 4 cases, cardiovascular abnormalities were detected by clinical, electrocardiographic or radiological examination in the following 19 cases:

(a) Case 36, aged 62, had a soft systolic murmur at the apex and the T wave was inverted in Lead IVR. The blood pressure was normal.

(b) Case 69, a female aged 60, had essential hypertension. (230/120) mm. Hg.) The T wave was inverted in Leads 11, CF_2, CF_4 and CF_5.

(c) Case 14, aged 63, had essential hypertention (180/100 mm. Hg.) The electrocardiogram showed the presence of left ventricular strain.

(d) Case 67, aged 77, had identical features to those found in Case 14 and, in addition, there was left ventricular enlargement radiologically.

(e) Case 37, aged 62, had a systolic murmur at the aortic area conducted down the left side of the sternum. The T wave was inverted in CF_2, CF_4 and CF_5. There was no cardiac enlargement radiologically.

(f) Case 26, aged 53, had essential hypertension (194/104 mm. Hg.) Clinical features of congestive cardiac failure were present for the...../

the past 2 years. The electrocardiogram, recorded after digitalisation, showed depression of the ST segment in Leads 1, 11, 111 and IVR. The radiological examinations showed that the lung fields were congested but there was no evidence of cardiac enlargement.

(g) Case 3, aged 57, had a loud systolic murmur at the apex conducted to the axilla. The T wave was inverted in Leads 1, 11 and 111. The heart was displaced to the left, clinically and radiologically, by left-sided pulmonary fibrosis of undetermined etiology.

(h) Case 56, aged 70, had a soft systolic murmur at all areas. The QRS complexes were broadened to 0.11 secs. and were notched to an abnormal degree.

(i) Case 24, aged 17, had a soft, systolic murmur at all areas and the T wave was inverted in CF_4. The left border of the heart was "straightened" as a result of an attack of acute rheumatic pleurisy one year previously.

(j) Case 65, aged 60, had a PR interval 0.21 secs. in duration. The aortic knuckle was prominent radiologically.

(k) Case 62, aged 52, showed inversion of the T wave in 4R, CF_4 and CF_5.

(l) Case 49, aged 39, had frequent ventricular extra-systoles, detected clinically and electrocardiographically.

(m) Case 60, aged 31, had inversion of the T wave in Lead 1.

(n) Case 6, aged 78, had essential hypertension (150/100 mm. Hg.) and gross arteriosclerosis. The left ventricle was enlarged and the aortic knuckle was calcified on radiological examination.

(o) ...../

(o) and (p) Cases 58 and 63, aged 66 and 69, both had essential hypertension (220/130 and 240/130 mm. Hg. respectively) with signs of congestive cardiac failure. The radiological examinations in Case 58 showed left ventricular enlargement and pulmonary congestion.

(q), (r) and (s) Cases 10, 12 and 20, (aged 51, 51 and 46) had soft systolic murmurs at the apex.

.. ..

This data represents the "positive" findings. In the remainder of the cases studied there were no signs of clinical, electrocardiographic, phonocardiographic or radiological abnormalities of the heart. The pulse was regular in rhythm in all 70 cases studied. Evidence of arteriosclerosis of the radial and fundal arteries was detected in many of the more elderly patients in the series, and unfolding of the aorta was noted radiologically in 12 of the cases examined. The phonocardiographic studies failed to reveal the presence of any diastolic murmurs which were not detectable on clinical examination.

C. DISCUSSION.

Unquestionable evidence of valvular disease was detected in 4 of the 70 cases. The diagnosis was based in each instance on the presence of a characteristic diastolic murmur. Each special investigation (radiographical, electrocardiographic and phonocardiographic) was not performed in all the 4 cases, but where an investigation was performed it confirmed or supported the clinical diagnosis.

Of the 4 cases, 2 had aortic regurgitation and mitral stenosis; one had mitral stenosis alone and one had aortic regurgitation alone. The etiology of the latter case could, of course, not be proved with absolute certainty, but the Wasserman reaction was negative and there were no other features of syphilis. There were thus 3 proved cases and one very probably case of rheumatic valvular disease in this series - an incidence of approximately 6 per cent. The sudden onset of the gangrene of both feet in Case 2 with aortic regurgitation suggested the occurrence of bilateral simultaneous embolism of both femoral arteries or of the lodgement of a "rider-embolus" at the bifurcation of the aorta. However there were certain difficulties, viz. the absence of mitral stenosis and of auricular fibrillation, and it was not possible to reach a final conclusion.

.. ..

The results of the investigation in the other cases listed above were unimpressive. A few cases had congestive cardiac failure and many had electrocardiographic abnormalities, but the majority of these cases had a probable etiological condition - essential hypertension. Electrocardiographic abnormalities in some cases, e.g. Case 65, were so slight, that they could even be regarded as still within possible normal limits, while electrocardiographic abnormalities in other cases, e.g. in Case 56 (intraventricular block) and in Case 37 (T wave inversion) could reasonably be ascribed to coronary sclerosis in elderly patients. Systolic murmurs, where audible, were soft in intensity and could usually be related to the presence of hypertension or cardiac displacement. Only in Case 24, a patient aged 17, with a past history of rheumatic fever and in Case 60, aged 31, was the inversion of the T wave suggestive of cardiac disease or disorder.

.. ..

CONCLUSION.

There were 4 cases of valvular heart disease (probably of "rheumatic" type) detected with certainty in this series of 70 cases - an incidence of about 6 per cent. This finding is in conformity with the hitherto-reported low incidence of "clinical" rheumatic heart disease in cases of rheumatoid arthritis, in spite of the frequency of rheumatic heart disease found at autopsy.

Certain interesting conclusions may, however, be drawn from the investigations.

1. The occurrence of 4 instances of valvular heart disease in 70 cases of rheumatoid arthritis indicates that there is clinical evidence of the rheumatic heart disease in a small, but significant number of cases in a large series of unselected cases of rheumatoid arthritis.

2. In spite of careful and intensive clinical and electrocardiographic observations on the remainder of the 70 cases, combined with very good facilities for radiological examination, it was not possible to demonstrate the presence of rheumatic heart disease with the frequency demonstrable at autopsy. The problem of the reconciliation of this apparent discrepancy remains unsolved.

Whenever features of congestive cardiac failure, cardiac enlargement or electrocardiographic abnormalities

were...../

were encountered, they could in nearly all cases be explained readily by the coincidental presence of hypertension, arteriosclerosis or cardiac displacement.

None of the cases showed auricular fibrillation or other significant arrhythmias. The ventricular extrasystoles in Case 49 were unassociated with signs of cardiac disease.

It was hoped that phonocardiograph investigations, with the aid of special postures, etc. might result in the detection of a greater number of diastolic murmurs than those detected clinically, but the results did not prove of value.

SECTION V.

THE NEUROMUSCULAR SYSTEM IN RHEUMATOID ARTHRITIS.

A. REVIEW OF THE LITERATURE.

MILLER (1936) stated that there was "no satisfactory explanation" for the selective and marked muscle atrophy which occurred in most cases of rheumatoid arthritis. He noted that the muscular atrophy might continue to progress after all evidence of inflammation in the joints had subsided. The Committee of the American Rheumatism Association ("Primer on Arthritis", 1942) also discussed the problem of the causation of the prominent muscular weakness and atrophy in the disease. In some cases these muscular features were the most striking features of the entire symptomatology. They noted that the atrophy was particularly noticeable in the hand muscles but also occurred in all muscles of the extremities and contributed to the fusiform appearance of the joints. They considered that the muscular atrophy was an integral part of the disease and was not attributable to disuse alone.

Paraesthesiae are commonly present in the extremities in rheumatoid arthritis and other features resembling neurological disorders may occur. The tendon jerks in the limbs may be unobtainable on account of extensive articular and periarticular fibrosis. In other cases again the tendon jerks are very brisk and may be accompanied by pseudo-clonus or even by sustained clonus. The neurological features (wasting, brisk tendon jerks, clonus and paraesthesiae) may be so prominent that

rheumatoid ...../

rheumatoid arthritis may simulate Motor Neurone Disease. The contractures which occur in rheumatoid arthritis may erroneously be regarded as a deformity due to paraplegia-in-flexion.

Many cases in this series had these clinical features suggestive of neurological disorders and Case 23 was actually admitted to the neurological wards in the first instance.

.. ..

Recently certain pathological investigations have indicated that there is frequently widespread involvement of the neuromuscular system in rheumatoid arthritis, and it has been suggested that this may be responsible for the prominent neuromuscular clinical features.

CURTIS and POLLARD (1940) were the first to describe a nonarticular lesion which was common to all their 11 cases of rheumatoid arthritis including 4 cases with "Felty's Syndrome". In every one of their 11 cases the authors found small perivascular infiltrations with lymphocytes in the muscles.

FREUND, STEINER, LEICHTENTRITT and PRICE (1942a, 1942b) undertook an autopsy investigation of the central and peripheral nervous system in cases of rheumatoid arthritis and their results proved highly interesting. They examined only the brain and spinal cord at the beginning of their investigation but no specific or characteristic lesions were found. In their subsequent cases the peripheral nerves were studied in addition

in ...../

in 5 cases. They selected for examination the peripheral nerves which could be removed fairly easily at autopsy, e.g. axillary, sciatic, tibial and femoral nerves. Only nerve trunks were examined; the more peripheral portions close to the joints were not examined.

In each of the 5 cases similar changes were found. The principal characteristic finding was a nodular inflammatory lesion which the authors termed "rheumarthritic nodulous perineuritis". They considered that the term "nodulous" was justifiably used as the lesions were sharply circumscribed in appearance and were sharply demarcated from the surrounding perineural tissue which was perfectly normal. Some of the nodules consisted solely of lymphocytes while others also contained a variable number of epithelioid cells. A central acellular zone of homogenous material and nuclear debris was sometimes present. In some nodules there were 3 well-defined zones: a central zone of necrosis; an intermediate zone of proliferating mesenchymal epithelioid cells and a peripheral ringlike zone of lymphocytes and plasma cells. This histological appearance somewhat resembled the structure seen in the subcutaneous nodules but there was no close similarity. These nodules were found to be scattered at different sites along the longtitudinal course of a peripheral nerve. They were found in groups of 3 or 4 in the same section and the adjacent blocks or the same nerve might be free of these nodular lesions. In 3 cases the nodules were numerous and in 2 cases the

nodules were smaller and less numerous. The nodules in each case were situated exclusively in the perineurium, and the authors stressed the fact that the adjacent nerve fibres and myelin sheaths were normal throughout in all respects.

These authors also examined the peripheral nerves of 86 control cases in order to establish the specificity of the pathological observations. The series included 2 cases of rheumatoid arthritis and characteristic nodules were encountered in one of the cases but were not found in the second case. Two cases of dermatomyositis in the series showed changes interpreted as a primary myositis in which the inflammatory cells invaded the adjacent epineurium and perineurium. One case of Post-encephalitic Parkinsonism showed a diffusely-spread endoneural inflammatory infiltration with lymphocytes, which was designated as "Diffuse lymphocytic Endoneuritis" and which was regarded as entirely different from the "Nodulous Perineuritis" observed in rheumatoid arthritis; one case of broncial carcinoma had metastases in the femoral nerve and a case of Thromboangeitis Obliterans had distinctive vascular changes, but none of the controls without rheumatoid arthritis showed the characteristic lesions which were described in the 5 cases above. The authors thus considered that there were strong grounds for suggesting that the changes in the peripheral nerves in rheumatoid arthritis were specific.

They ...../

They also referred to KOEPPEN's observations (1932) that he had found normal sciatic nerves in 2 cases of "Arthritis Deformans", and that he had found circumscribed perivascular lymphocytic infiltrations in the endoneurium (or more rarely in the perineurium) in 3 of 7 cases with rheumatic fever. There were no cases of active rheumatic fever in the control cases examined by FREUND, STEINER, LEICHTENTRITT and PRICE (1942a, 1942b).

.. ..

In 1946, STEINER, FREUND, LEICHTENTRITT and MAUN examined the muscles from 9 cases of rheumatoid arthritis. Muscle biopsies were taken from the gastrocnemius in 4 cases and from the triceps and deltoid in 2 cases. In one case muscles from the legs were examined after a midthigh amputation and in 2 cases muscles were obtained at autopsy. The authors were impressed with the marked and sometimes rapidly-progressive character of the muscular wasting in rheumatoid arthritis and were searching for anatomopathological changes to which the muscular atrophy could be related. The specimens of muscle examined varied in length between 0.3 cm. and 1.6 cm., and in thickness between 0.29 cm. and 0.9 cm., i.e. they were usually small in size.

Inflammatory nodules were found in each of the cases. They were situated in the perimysium and in the endomysium ...../

endomysium, rarely in the epimysium. The nodules consisted of collections of lymphocytes and plasma cells and the authors termed the lesion "Nodular Polymyositis". Not every muscle examined contained these inflammatory nodules but they were present in at least one or more muscles in each of the 9 cases, and multiple nodules were often present in one piece of muscle. As only small amounts of muscle taken at random were examined, the results indicated the widespread involvement of the skeletal muscular system by "nodular polymyositis". The size of the nodules varied from very small ones (consisting of "20 or less lymphocytes") to large ones visible to the naked eye in the stained sections. The shape was round or oval, triangular or spindle-shaped, often elongated with processes of cells infiltrating the endomysium between 2 or more muscle fibres.

The authors commented that the muscular lesions fitted "into the general pattern of the other lesions" in rheumatoid arthritis and that there was striking similarity between the lesions noted in the synovial membrane, in the subcutaneous nodules, in scleromalacia perforans, in the nerves and in the muscles in the disease.

Lesions were found in muscles which were not adjacent to affected joints, e.g. in the rectus abdominis, so that the authors concluded that the lesions were not the result of any local arthritic disturbance.

Perineural...../

Perineural inflammation of small intramuscular nerves was often noted but they were satisfied that the vast majority of the muscle lesions were "autochthenous" and not secondary to perineuritis.

They also described an interesting finding which they claimed had not been previously reported. Definite arteritis and periarteritis could be seen in the small muscular vessels in some of their cases. This finding indicated that the vascular lesions in rheumatoid arthritis were not confined to the joints or subcutaneous nodules.

The authors made the interesting observation that inflammatory foci were present in the muscles and in the perineurium of the nerves even in old-standing cases of rheumatoid arthritis which were "seemingly burnt-out"! They concluded that the thrminal stage of rheumatoid arthritis without pain and with extreme stiffness of joints and bony deformities was deceptive since active inflammatory processes were detectable in the muscle and nerves, and that the disease was therefore "smouldering" even in its later stages. These observations are particularly interesting in view of the detection of elevation of the sedimentation rate in several of the apparently "burnt-out" cases in this series.

In addition to the nodular inflammatory lesions the authors also noted the occurrence of various stages of degeneration and atrophy of the muscle fibres with

proliferation...../

proliferation and increase in size of the nuclei. Inflammatory changes occurred in some cases without degenerative changes, whereas early degenerative changes were always combined with inflammatory endomysial lesions in some fibres. Degenerating muscle fibres were sometimes found in intimate relationship with "nodular polymyositis" foci. The authors thus concluded that the degenerative changes, if present, were always secondary to the inflammatory changes.

Muscles were also examined in a series of controls from 196 routine autopsies. One case of dermatomyositis and one case of trichiniasis had widespread inflammatory muscular changes, not nodular in appearance. Muscular degeneration, without inflammatory lesions, was found in cases of amyotrophic lateral sclerosis, myotonia congenita and muscular dystrophy. "Nodular polymyositis" thus appeared to be a specific feature of rheumatoid arthritis.

The authors concluded by suggesting that the anatomopathological lesions described above, rather than disuse, were responsible for "the clinical picture of muscular atrophy in rheumatoid arthritis" and indicated the probable future value of muscle biopsy in the diagnosis of the disease and in the control of its therapy.

KERSLEY ...../

KERSLEY (1945) reviewed these reported observations and noted that the lesions described appeared to be specific to rheumatoid arthritis.

GIBSON, KERSLEY and DESMARAIS (1946), by muscle biopsies, confirmed the presence of the lesions described by STEINER, FREUND, LEICHTENTRITT and MAUN (1946). They found nodular inflammatory lesions in each of 11 cases of rheumatoid arthritis. They described perivascular cellular reactions in the muscles and paravascular lesions in the fibrous, and fatty, connective tissue. They also confirmed the observations that similar changes were found in active and in quiescent cases, irrespective of whether they had received gold or not, and agreed that the condition must be very widespread as lesions were found in specimens removed at biopsy from a variety of muscles selected at random. Degenerative changes were also noted in the muscles but their extent did not always closely parallel the extent of the inflammatory changes.

MORRISON, SHORT, LUDWIG and SCHWAB (1947) examined the central nervous system at autopsy in 44 cases of rheumatoid arthritis and in a control group of 50 cases of similar age distribution without rheumatoid arthritis. They found nodular lesions in the peripheral nerves in 26 out of 31 cases which they examined, similar to the lesions described by FREUND, STEINER, LEICHTENTRITT and PRICE (1942). They differed, however, in claiming

that...../

that they recognised atrophy of the axons and of the myelin sheaths in the affected nerves. They also stated that they had demonstrated "retrograde degeneration" in the corresponding anterior horn cells. They encountered alterations in skeletal muscle in 8 out of 14 cases. The lesions varied from definite nodular forms to smaller collections of lymphocytes and plasma cells which were often seen in relation to bloodvessels. Degenerative changes in the muscle fibres themselves were frequently noted.

In their control series of cases "closely-corresponding lesions" were found in the muscle and in the nerves in a few cases of dermatomyositis, disseminated lupus erythematosis and of scleroderma. They have therefore hesitated to describe the nodular inflammatory lesions seen in rheumatoid arthritis as necessarily specific.

de FOREST, BUNTING and KENNEY (1947) performed muscle biopsies (on deltoid or gastrocnemius muscles) on 16 cases of rheumatoid arthritis and found the characteristic lesions in 12 cases. Biopsies were also performed on 15 control patients, including cases of osteo-arthritis, rheumatic fever, gonococcal arthritis and 4 cases of "nonspecific infectious arthritis". Lesions were found in 2 of the 4 cases of "nonspecific infectious arthritis", in one case of osteo-arthritis which "had a history suggestive of rheumatoid arthritis" and were absent from all the other controls. They

remarked...../

remarked that these findings were further evidence that "there is little reason for separating nonspecific infectious arthritis from rheumatoid arthritis with predominantly atrophic changes".

They had "little difficulty" in finding the characteristic lesions in the muscle biopsy specimens. They "turned over" the blocks of tissues in their "negative cases" and cut sections from the other side, and in one of their original "negative" cases, they were able to demonstrate the changes by this means.

DESMARAIS (1948) reported the results of a further series of 95 cases in which muscle biopsies were performed. Of the 35 cases of rheumatoid arthritis, 28 biopsies showed typical round cell foci and 7 were "negative". One case was "negative" at biopsy, but proved to be "positive" when a large piece of muscle was excised at operation. The remaining 60 cases covered a wide range of other types of rheumatic and non-rheumatic conditions (including 12 cases of ankylosing spondylitis, 4 of gonococcal arthritis, 2 of "Still's Disease" and 4 of osteo-arthritis) and were all "negative".

.. ..

There are 2 important conclusions which may be drawn from the investigations reported above:

1. Muscle ...../

1. Muscle Biopsies, performed on a variety of muscles, have revealed the presence of inflammatory nodules in a high proportion of cases of rheumatoid arthritis. The nodules were small or large but all the investigators apparently detected their presence with great facility. Table 11 illustrates the results of the muscle biopsies performed by 4 of the above groups of workers.

TABLE 11.

Results of Muscle Biopsy in Rheumatoid Arthritis.

Investigators	Cases	"Positives"	"Negatives"
STEINER et al	7	7	-
GIBSON et al	11	11	-
de FOREST et al	16	12	4
DESMARAIS	35	28	7

It can be seen that "positive" results were obtained in 58 out of 69 cases by means of muscle biopsy. As only small portions of muscle were removed for examination the results are very striking as they indicate that the muscular lesions must be very widespread in the disease.

2. The results of the muscle biopsies performed on other cases as controls were almost all "negative".

de FOREST ...../

de FOREST et al examined 15 "controls" and DESMARAIS 60 "controls", and they reported the absence of the characteristic nodules. The only muscular lesions noted in the controls were obtained in a few cases of "non-specific infectious arthritis" and a case of "osteo-arthritis which had a history suggestive of rheumatoid arthritis".

It thus appeared that the presence of the inflammatory nodules was highly characteristic, and probably diagnostic of rheumatoid arthritis.

The "control" muscles examined by STEINER et al (1946) and by MORRISON et al (1947) were obtained at <u>autopsy</u>, and their results corresponded more or less with the findings of the above biopsy investigations. Their "control" cases were all "negative" with the exception of a few cases of dermatomyositis, disseminated lupus erythematosis, scleroderma and trichiniasis in which "closely-corresponding lesions" were found.

Even if dissimilar, or similar, inflammatory lesions do occur in these latter diseases, the value of muscle biopsy in the diagnosis of rheumatoid arthritis still remains as it would narrow the possibilities down to a "group" of diseases.

.. ..

However, CLAWSON, NOBLE and LUPKIN (1947) have reported results which, if correct, are largely irreconcilable with the findings of all the previous investigators. They performed muscle biopsies (in the deltoid muscles) in 44 cases of rheumatoid arthritis and found characteristic lesions in 17 cases (38.6 per cent) of the series. This is a lower incidence than was encountered by other biopsy studies but it nevertheless still indicates the presence of inflammatory foci in a considerable number of cases.

The results of their biopsy examinations on their control cases have been very surprising. Seven muscles were collected from each of 450 autopsies and were studied for evidences of inflammation and various stages of degeneration. In 118 cases (i.e. 26.2 per cent of the 450 cases) inflammatory lesions were observed of one or more grades and in one or more muscles! They divided their inflammatory lesions into 4 grades - Grade 4 resembled a large nodule (as illustrated in STEINER et al's photographs, 1946), and Grade 1 resembled a small nodule (as illustrated in STEINER et al's photographs). They noted "positive" results in a wide variety of diseases - acute rheumatic fever, bacterial endocarditis, hypertension, coronary sclerosis, accidents and trauma, "tumors", cerebral haemorrhage, cirrhosis, "gastrointestinal conditions", tuberculosis, poliomyelitis, pneumonia...../

pneumonia, infections of the bladder and kidneys, etc.

These results, if correct, challenge the validity of the results reported by STEINER et al (1946), GIBSON et al (1946), DESMARAIS (1948) de FOREST et al (1947) and MORRISON et al (1947).

It is difficult to find a possible source of error in CLAWSON et al's investigations (1947). They admitted that "rheumatoid arthritis may have been present to some extent without being mentioned in the histories" in some of their cases, but statistically, it is very improbable that coincidental rheumatoid arthritis was present in more than a fraction of the cases.

Nor can it be said that the criteria employed by CLAWSON et al (1947) in their diagnosis of "positives" were very different from those employed by former workers. They specifically stated that they did not regard "the presence of but a few lymphocytes" as indicating a "positive result". Their illustrations of "positive results" appear similar to those shown by previous investigators. Most of their "positive" results were grouped in Grades 1 and 2, but many were grouped in Grades 3 and 4. CLAWSON et al (1947) also commented that the lesions were found more frequently in cases in which death occurred in the upper decades of life.

Yet...../

Yet in an extensive examination of muscles in "control" cases including approximately 70 muscle biopsies and the examination of muscles of approximately 250 cases at autopsy), STEINER et al (1946), de FOREST et al (1947), MORRISON et al (1947) and DESMARAIS (1948) noted no "positive" results (with the exception of the few cases of dermato-myositis, etc. mentioned above).

How are these diverse results to be reconciled? It is possible that CLAWSON et al (1947) detected the high incidence of muscle lesions in numerous diseases on account of their extensive examinations on 7 muscles at each of the 450 autopsies, whereas the other observers have examined only smaller pieces of muscle removed by biopsy or at autopsy.

The conclusion must, however, be drawn that the problem is unsolved. If CLAWSON et al (1947) are correct in their observations, then they constitute a very serious obstacle to the claims that these inflammatory nodular foci found in muscle in cases of rheumatoid arthritis are in any way diagnostic of the disease.

B. RESULTS OF THE PRESENT INVESTIGATION.

Deltoid muscle biopsies were performed in 34 cases of the 70 cases in this series. In 14 cases characteristic inflammatory lesions were found in the sections and the findings are described in detail in Table 12. The muscle biopsies were "negative" in the remaining 20 cases. (Cases 1, 2, 5, 9, 10, 13, 16, 17, 24, 27, 29, 35, 37, 43, 46, 51, 61, 62, 65 and 67).

The number of inflammatory foci (nodules) detected in the "positive" sections varied from one to 7. Single foci were present in 6 sections and multiple foci in the other 8 sections.

During the microscopical examination of the sections attention was chiefly focussed on the inflammatory changes rather than on the degenerative and atrophic changes in the muscle. It was sometimes difficult to distinguish with certainty between degenerative changes in the muscle and changes resulting from the trauma of removal. As the inflammatory changes, not the degenerative changes, are the ones which have been regarded as probably of diagnostic value in the disease, it is not of great consequence if the degenerative, atrophic changes are mentioned more briefly.

TABLE 12 ...../

TABLE 12.

RESULTS OF 14 "POSITIVE" DELTOID MUSCLE BIOPSIES.

Case	Duration of Arthritis.	Number of Nodules.	Description of Inflammatory Nodules.
7	3 years	3	One small nodule consisted of about 40 cells and 2 larger nodules consisted of about 100 cells each. They were all situated in the endomysium and 2 of these nodules were perivascular in distribution. The cells were practically all lymphocytes. The nodules were more or less oval in shape.
69	7 years	1	It was a small nodule consisting of about 50 lymphocytes, situated in the endomysium at the edge of the section.
64	20 years	1	The nodule consisted of a focus of about 50 small round cells (mostly lymphocytes with a few plasma cells). Eosinophilic stands of tissue were present in the nodule and appeared to be remnants of muscle tissue. A few large nuclei were present in the focus and may have originated from the sarcolemmal sheath. Atrophic muscle fibres were encountered at the edge of the nodule.

Page 2 ...../

Page 2. Table 12.

Case	Duration of Arthritis.	Number of Nodules.	Description of Inflammatory Nodules.
53	5 years	7	A very extensive lesion was present. Four tiny blue foci were visible in the section on naked-eye examination. They varied in size from a pinhead to a pinpoint. Seven foci were readily identified microscopically. They consisted of small round cells, chiefly lymphocytes with a few plasma cells, but in one focus plasma cells were the predominant cell. Scanty eosinophils were present in the nodules. The shape of the nodules varied - some were oval, others elongated and several were fusiform. The nodules varied in size. One nodule was very large and replaced a large area of muscle (Fig. 88). It was situated in the endomysium and collections of cells straggled out from the main nodule between adjacent muscle fibres. A few small portions of muscle fibre were isolated in the centre of this large focus. A second nodule was about half the size of this large nodule, while an oval-shaped third nodule was about one-third the size of the large nodule (Fig. 90). Fragments of muscle were recognisable in the centre of this latter nodule. 4 smaller nodules, each consisting of about 100 cells, are present ...../

Page 3. Table 12.

Case	Duration of Arthritis.	Number of Nodules.	Description of Inflammatory Nodules.
			present in the endomysium and were perivascular in distribution. The bloodvessel was usually situated near the one end of the nodule, not in its centre. There were a few atrophic muscle fibres but atrophy was not a marked feature of the sections in spite of the very extensive inflammatory changes.
70	12 years	5	Extensive lesions were present, but not to quite the same degree as in Case 53 above. Four of the nodules could be identified in the sections with the naked eye. The nodules were mainly situated in the endomysium; one nodule was situated in the perimysium. Only one of the 5 nodules was perivascular in distribution; the others were not related to any blood vessels. They were chiefly spindle-shaped in this section (Fig. 91). In one area the cells could be seen surrounding the muscle fibres in transverse section (Fig. 92). The size of the nodules varied; the smallest nodule consisted of about 100 cells while the largest contained several hundred cells. Lymphocytes comprised the vast majority of the cells in each case. The muscle fibres often showed fragmentation..../

Page 4. Table 12.

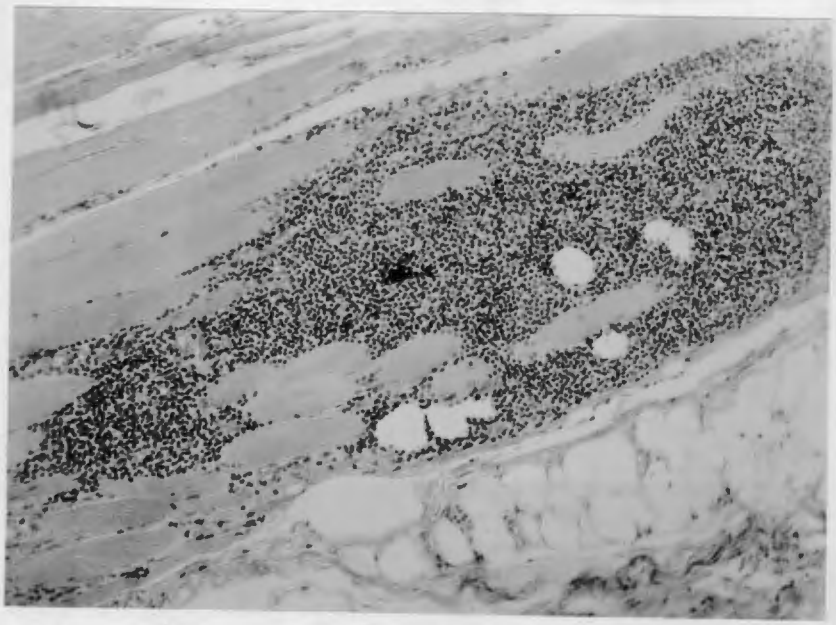
Case	Duration of Arthritis.	Number of Nodules.	Description of Inflammatory Nodules.
			fragmentation at the sites of the cellular infiltration. This patient also had Paget's Disease of both tibiae. (Fig.93).
21	8 years	1	One irregularly-shaped perivascular nodule was present in the perimysium. It consisted of about 75 cells. The majority were lymphocytes. Several polymorphs were present but appeared to be lying in the of the blood vessel.
54	6 years	2	The nodules were small and each consisted of about 45 small round cells situated in the endomysium.
3	8 years	6	Six small nodules were present in the endomysium. Each consisted of about 40-60 small round cells. The nodules were perivascular in distribution in 3 instances.
51	12 years	2	Two large triangular perivascular nodules were easily detected in the perimysium. They each consisted of about 200 cells which were chiefly lymphocytes. A few macrophages and plasma cells were also present. An occasional arteriole in other parts of the section showed some slight perivascular infiltration with about 10-15 lymphocytes. Scanty round cell infiltration was present between some muscle fibres.

Page 5. Table 12.

Case	Duration of Arthritis.	Number of Nodules.	Description of Inflammatory Nodules.
32	2 years	6	Six small nodules, consisting of 30-60 small round cells, were detected in the endomysium and in the perimysium. They were almost all perivascular in distribution and the blood vessel was situated near an edge of the nodule.
4	1 year	4	One nodule consisted of about 80 small round cells while the other 3 were smaller and each consisted of 30-40 cells. The larger nodule was perivascular in its situation. The smaller nodules were seen encircling individual muscles in transverse section.
20	8 years	1	A spindle-shaped nodule consisting of about 80 lymphocytes was present in the endomysium adjacent to a small blood vessel.
25	1 year	1	A small irregularly-shaped collection of about 40 small round cells was seen encircling a muscle fibre. The appearance was similar to that seen in Fig. 92
56	4 years	1	A small nodule consisting of about 45 small round cells was present in the perimysium adjacent to a small blood vessel.

FIG. 89.

Deltoid Muscle Biopsy.



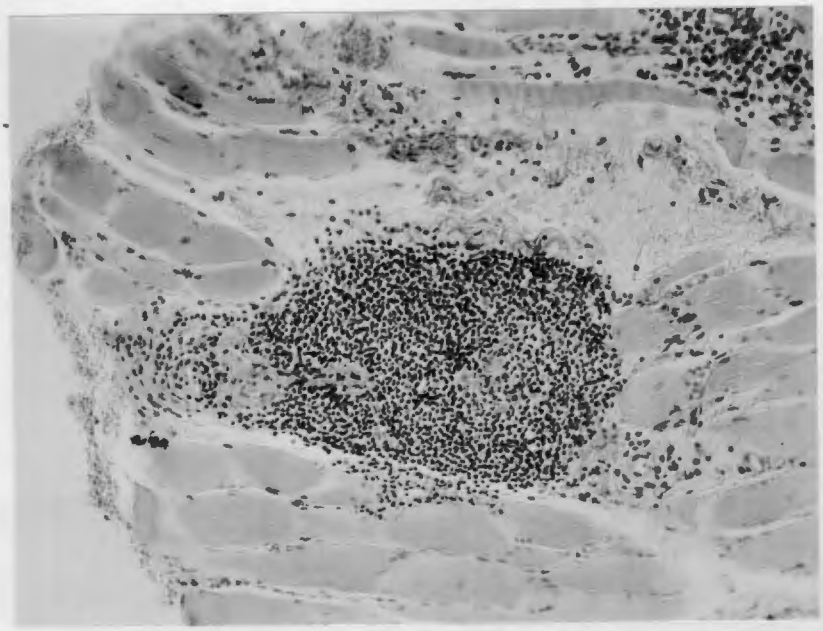
Case 53 : Rheumatoid Arthritis.

Very extensive small round cell infiltration which is partly separating and partly replacing muscle fibres. Note that small projections extend from the large nodule into the adjacent muscle.

(H. & E. x 130).

FIG. 90.

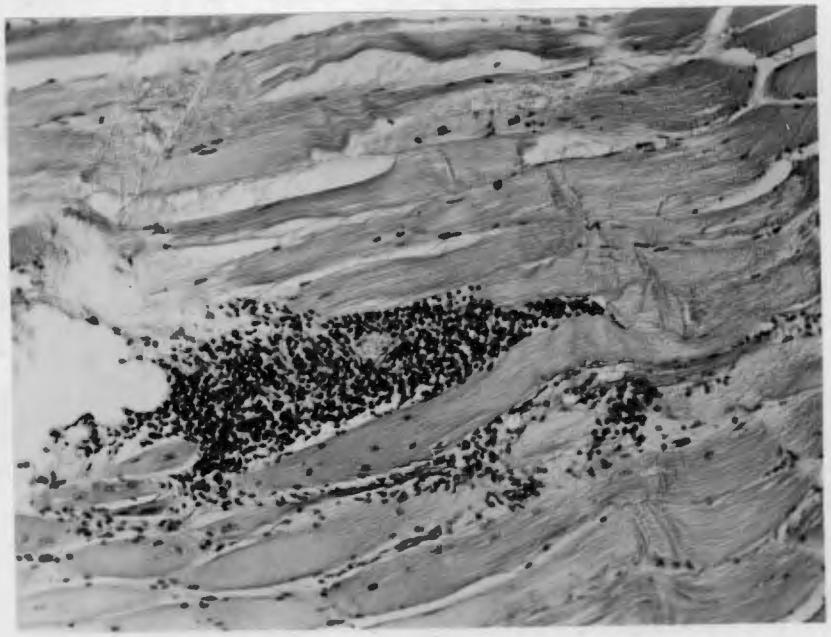
Deltoid Muscle Biopsy.



Case 53 : Rheumatoid Arthritis.
Large oval nodule of small round cells situated adjacent to a very small bloodvessel. The muscle fibres terminate at the edges of the nodule and fragments of atrophied muscle can be detected within the nodule.
(H. & E. x 130).

FIG. 91.

Deltoid Muscle Biopsy.



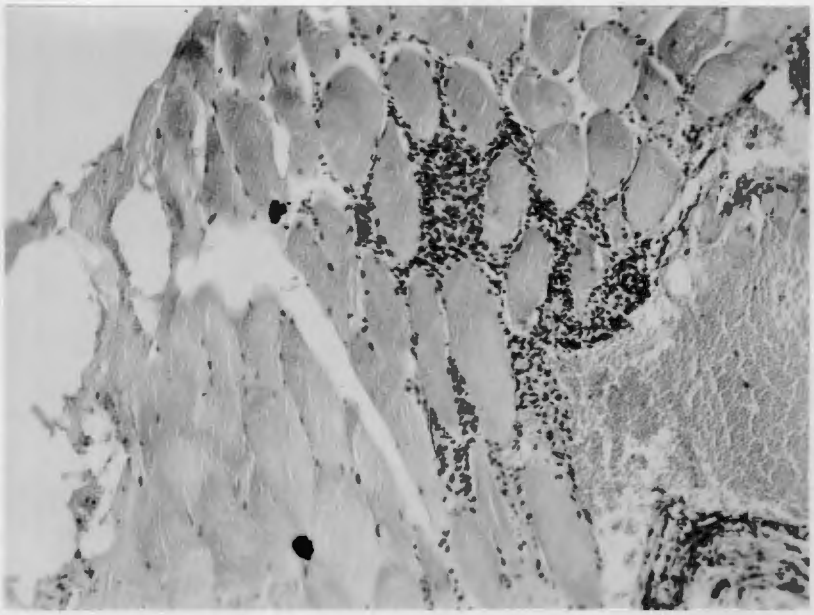
Case 70 : Rheumatoid Arthritis.

Longtitudinal section through muscle fibres.
Triangular-shaped nodule of perivascular infiltration of small round cells which separates adjacent muscle fibres.

(H. & E. x 130).

FIG. 92.

Deltoid Muscle Biopsy.



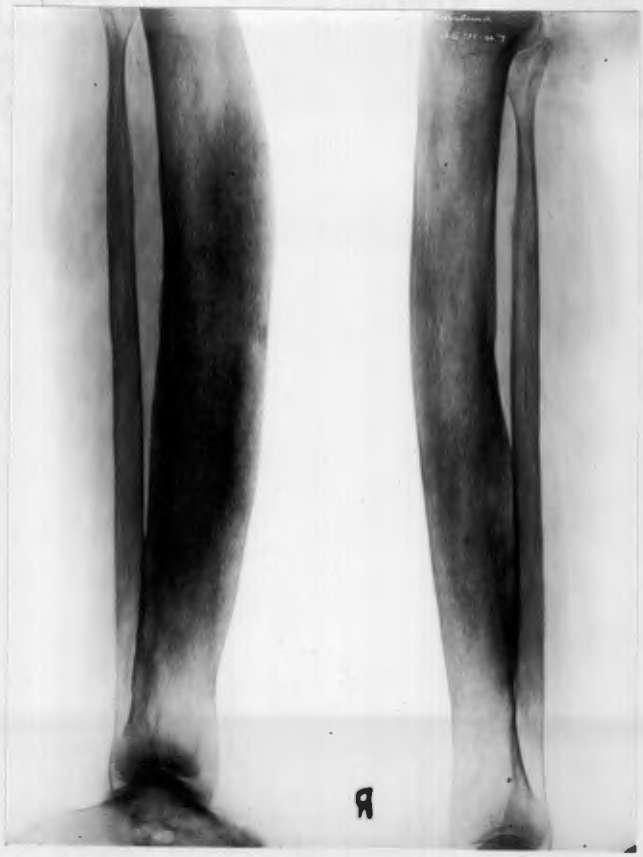
Case 70 : Rheumatoid Arthritis.

Transverse section through muscle fibres with small round cell infiltrations surrounding individual muscle fibres.

(H. & E. x 130).

FIG. 93.

Radiological Appearances of Tibiae.



Case 70 : Rheumatoid Arthritis with Paget's Disease.

The characteristic radiological appearances of Paget's Disease of the tibiae is illustrated. Its occurrence in the case appears fortuitous.
The histological appearances of the deltoid muscle biopsy are illustrated in Figs. 91 and 92.

C. DISCUSSION.

The results of the deltoid muscle biopsies were "positive" in approximately 40 per cent of the 34 cases examined. These findings thus confirm the reported incidence of the inflammatory foci and nodules in the muscle in rheumatoid arthritis. The incidence encountered in this series is lower than that noted by most of the investigators but is nevertheless a very substantial percentage.

A striking feature is the ease with which the inflammatory nodules could be recognised and identified. They appeared in sharp contrast to the surrounding muscle fibres and could be easily detected. In 2 cases (Cases 53 and 70) the nodules were sufficiently large to be visible in the sections on naked-eye examination.

The nodules varied in size from small foci consisting of approximately 30 small round cells (which would constitute "Grade 1" in CLAWSON et al's classification) to very large nodules (which would constitute "Grade 4 in their classification). Fig. 89 illustrates the appearance of such a very large nodule while Fig. 92 illustrates a collection of cells somewhat larger than a "Grade 1" nodule.

The shape of the nodules varied; some were round, others triangular, others oval, others elongated, and others spindle-shaped. The edges sometimes "tailed off"

between ...../

between adjacent muscle fibres.

The nodules were encountered in the endomysium and in the perimysium. They were often perivascular or paravascular in situation but some nodules occured without any obvious relation to a blood vessel.

The cells consisted mainly of lymphocytes, with a variable number of plasma cells and a few eosinophils in some nodules. The muscle fibres at the edges of the larger nodules often showed atrophy and fragmentation. In some nodules muscular remnants could be still recognized. However, there was no close parallelism between the degree of inflammatory change and the degree of muscular atrophy; inflammatory change was very marked in Case 53 while atrophy was inconspicuous.

The conclusion, therefore, appears to be that one nodule, or multiple nodules, are commonly found in sections of muscle removed by biopsy in cases of rheumatoid arthritis. The results are all the more striking as only small portions of muscle were removed at biopsy and yet the lesions were readily detected in 40 per cent of the 34 cases examined. The histological findings in this series of 14 "positive" biopsies conform with the descriptions of "nodular polymyositis" given by STEINER et al (1946).

There did not appear to be any close relationship between the finding of a "positive" muscle biopsy and the degree of "activity" of the arthritis. Case 51, e.g. was clinically "burnt-out" and had a normal sedimentation rate, yet ...../

yet 2 large inflammatory nodules were seen in the muscle biopsy sections.

EXAMINATION OF "CONTROL" CASES.

However it must be realized that these results of the deltoid muscle biopsies confirm only one point, viz. the high incidence of "positives" in cases of rheumatoid arthritis. The other problem which arose from the review of the literature was whether these findings are specific to rheumatoid arthritis or whether they also occur in a variety of conditions.

It has already been pointed out that slightly similar or closely-similar histological appearances were noted in the muscles of some cases of dermato-myositis, scleroderma and disseminated lupus erythematosis. (MORRISON et al, 1947).

These observations do not greatly detract from the value of the muscle biopsy in rheumatoid arthritis as the diseases mentioned are, on the whole, rare, and the high incidence of "positives" amongst them might be an indication of a possible relationship between rheumatoid arthritis and a wider group of disseminated conditions.

The important problem arose from CLAWSON et al's claims (1947) that "nodular myositis" (of varying degrees) occurred in 26.2 per cent of a control series of 450 cases examined at autopsy! Their series of control cases was so large that correspondingly large series of further controls would be necessary before their claims could be disproved. On the other hand, an examination of smaller

groups ...../

groups of cases would nevertheless be of some value in accumulating data in regard to the incidence of "nodular myositis" in conditions other than rheumatoid arthritis. It has already been pointed out that DESMARAIS (1947) by biopsy examinations and MORRISON et al (1947) by autopsy examinations did not observe "nodular myositis" in the large group of diseases in which CLAWSON et al (1947) claimed to have found them.

Muscle biopsies from 12 cases (other than rheumatoid arthritis) were examined. The muscle examined was the deltoid in most instances. The diagnoses and the histological appearances are described in Table 13 Two of the cases died subsequently, and autopsy sections from several muscles were also examined.

In a further series of 8 cases, specimens of muscle were removed at autopsy and the sections were examined. The diagnoses and the histological appearances are described in Table 14 .

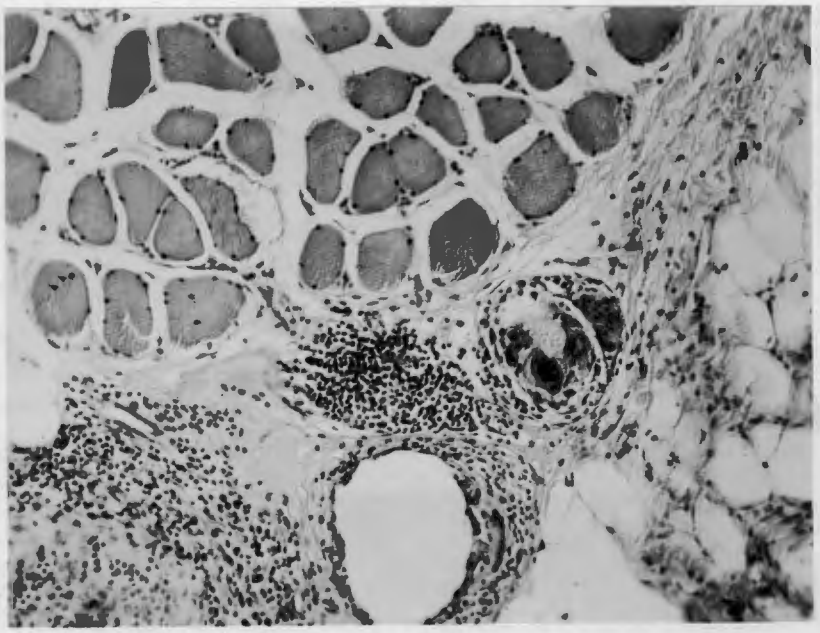
TABLE 13.

Examination of Muscle Biopsies from 12 "Control" Cases.		
Diagnosis.	Muscle.	Histological Appearances.
Acute Rheumatic Fever.	Deltoid.	Normal.
Osteoarthritis.	Deltoid.	Normal.
"Fibrositis".	Deltoid.	Normal.
Generalized Scleroderma.	Deltoid.	Normal.
Acute Rheumatic Fever.	Deltoid.	Normal.
Acute Diffuse Glomerulo-nephritis.	Deltoid.	Normal.
? Polyarteritis Nodosa.	Pectoral.	Normal.
Polyarteritis Nodosa.	Sacro-spinalis.	There was characteristic infiltration of the entire wall of a small artery with numerous polymorphs and inflammatory cells, but there were no foci of "nodular" myositis". At the subsequent autopsy only similar vascular lesions were found in other muscles.
Acute Poly-arthritis of unknown etiology. Complete recovery after 4 weeks.	Deltoid	Normal.

Diagnosis.	Muscle.	Histological Appearances.
Polyarteritis Nodosa.	Gastrocnemius.	Characteristic infiltration of entire wall of a small artery with inflammatory cells. There were no foci of "nodular myositis". (At the subsequent autopsy only similar vascular lesions were found in other muscles.
Gout (Case 83). (See Figs. 68 and 69 for histological appearances of tophus on ulnar border.)	Deltoid.	The histological appearances were very striking. 8 foci were present, each consisting of numerous small round cells. Numerous foreign body giant cells were present in some of the nodules. They were usually present at one edge of the inflammatory foci (as illustrated in Fig. 94), but were sometimes present amongst the small round cells. The inflammatory foci varied in size. The smallest ones consisted of about 30-50 cells while the largest focus consisted of several hundred cells One small focus was situated in the endomysium, but the majority of the foci were situated in the connective tissue on the surface of the deltoid extending into the epimysium and occasionally into the perimysium. (Fig. 95). Most of the foci were perivascular or paravascular whilst others were unrelated to blood vessel. There were no atrophic or degenerative changes in the muscle
Gout.	Deltoid.	Normal.

FIG. 94.

Deltoid Muscle Biopsy.



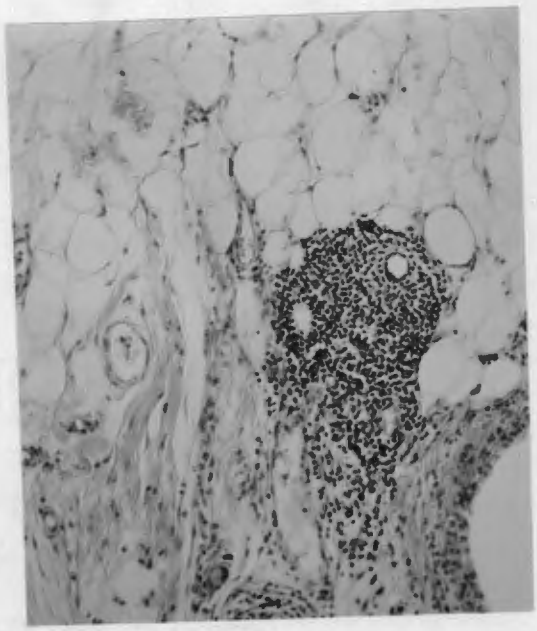
Case 83 : Gout.

Focus of lymphocytic infiltration adjacent to focus of small necrotic area with several giant cells. These foci are situated in the connective tissue adjacent to the muscle bundles.

(See Fig. 69 for nodule biopsy from same case).

FIG. 95.

Deltoid Muscle Biopsy.



Case 83 : Gout.
Nodular focus of small round cells in the fatty connective tissue adjacent to the muscle bundles. This is a different portion of the section of muscle illustrated in Fig. 94 .
The nodule resembles the inflammatory nodules noted in the muscle sections from cases of rheumatoid arthritis (See Figs. 90 and 91).

TABLE 14.

Examination of Muscle at 8 Autopsies.		
Diagnosis.	Muscle.	Histological Appearances.
Acute Porphyria.	Gastrocnemius.	Normal.
Miliary Tuberculosis.	Deltoid.	Normal.
Myocardial Infarction.	Deltoid.	Normal.
Trauma.	Deltoid.	Normal.
Miliary Tuberculosis.	Deltoid.	Normal.
Fractured Skull.	Deltoid.	Normal.
Generalized Peritonitis.	Deltoid.	Normal.

Although this series of control cases is admittedly small, it is interesting that (with 3 exceptions) no muscle lesions were encountered in the 12 muscles examined by biopsy and in the 8 muscles examined at autopsy.

Of the 3 cases with muscular lesions, 2 were cases of polyarteritis nodosa with characteristic vascular lesions and without evidence of "nodular myositis". (SELZER and HORWITZ, 1948).

The third case with vascular lesions had gout (Case 83); this is the case which had a subcutaneous tophus on the ulnar border (Figs. 68 and 69). When the deltoid muscle biopsy was performed the patient was suffering from an attack of gout in the knees and ankles for several weeks. The histological appearances were extremely interesting, (Figs. 94 and 95) and have not been hitherto noted in examinations of muscle biopsies. Some of the inflammatory foci closely resembled those seen in rheumatoid arthritis, but it was at once possible to differentiate the sections from those of the rheumatoid arthritis series by means of 2 features:

1. Numerous foreign-body giant cells were present in, or at the edge of, several of the inflammatory foci (Fig. 94). The lesions thus somewhat resembled those seen in the subcutaneous tophus (Fig. 69) and were

presumably ...../

presumably a tissue reaction to the local deposition of biurate crystals.

2. The majority of the inflammatory foci were situated in the connective tissue on the surface of the deltoid muscle, extending into the epimysium, and sometimes into the perimysium. The situation of the inflammatory foci were thus primarily in the subcutaneous tissue and the extension into the muscle (including the one endomysial focus) appeared to be secondary.

A deltoid muscle biopsy was then performed on another case of gout (Case 84 with large tophi on both ulnar borders - Fig. 71), but no lesions were found in the connective tissue nor in the muscle.

The "positive" result in the first case of gout is interesting as it probably indicated the deposition (in the past attacks or in the present attack of gout) of biurate in the deep subcutaneous tissue and in the intramuscular connective tissue. It is well-known that tophi may occur, not only in joints, cartilege, bursae and tendons, but also in subcutaneous tissue, and the histological appearances in this case probably represent a "microscopical tophus"!

As tophi only usually appear many years after the onset of gout, and as joint biopsy can only be undertaken in very few cases of gout on account of technical and practical difficulties, it may be that the biopsy of subcutaneous tissue and muscle in cases of suspected gout

might...../

might be of great diagnostic value. It is, of course, not possible to draw conclusions from one case, but further investigations of a series of cases of gout might indicate the utility of the procedure.

CONCLUSIONS.

1. "Positive" findings were obtained in muscle biopsies in 14 out of 34 cases of rheumatoid arthritis (40 per cent). This incidence is lower than that found by other observers and illustrated in Table 11 but corresponds with CLAWSON et al's (1947) incidence of 38.6 per cent "positives" in 44 biopsies.

2. There was no difficulty in determining the presence or absence of the inflammatory nodules in the sections and they were readily identified, sometimes even with the naked eye.

3. With the exception of a case of gout, examination of muscles (by biopsy or at autopsy) in a small series of 20 "control" cases did not reveal any cases of "nodular myositis". This finding, though far from conclusive, serves to confirm the findings of STEINER et al (1946), MORRISON et al (1947) and DESMARAIS (1948) in their examinations on "control" cases.

It has been noted, however, that if CLAWSON et al's (1947)observations are correct, then the incidence of "positives" in muscle biopsy in rheumatoid arthritis loses most, if not all, of its diagnostic significance.

4. A case of gout showed nodular foci of inflammation, mainly situated in the connective tissue and in the epimysium, and containing many foreign-body giant cells.

The ...../

The appearances could easily be distinguished from those seen in the muscle sections from rheumatoid arthritis. It is possible that biopsy of subcutaneous tissue and of muscle in suspected cases of gout may reveal information of diagnostic value.

D. THE CEREBROSPINAL FLUID IN RHEUMATOID ARTHRITIS

LUDWIG, SHORT and BAUER (1943) tested the cerebrospinal fluid of 59 cases of rheumatoid arthritis, and of 42 cases of spondylitis (with or without involvement of peripheral joints). They noted an increase in protein in 6.8 per cent of the 59 cases with only peripheral joint involvement, and in 28.6 per cent of the 42 cases with spondylitis. They considered that these abnormalities were due to alterations in serum proteins and to an increased permeability of meninges due to their proximity to joints affected by arthritis.

BOLAND, HEADLEY and HENCH (1947) studied the cerebrospinal fluid in 50 cases of rheumatoid spondylitis. 33 of these cases had spondylitis alone; 17 cases had associated rheumatoid arthritis involving the peripheral joints. They encountered no abnormalities in the cell and sugar content of the fluid. The total protein was increased in 21 cases, varying between 47 and 98 mg per cent. They observed that the average total protein tended to be higher in the severe, rapidly progressive cases than the average in the less severe cases. The protein content did not appear to be related to the duration of the disease, and was not increased more often

in...../

in cases with sciatica than in cases without sciatica. The protein was increased more often in cases with rheumatoid spondylitis and peripheral rheumatoid arthritis than in cases with rheumatoid spondylitis alone.

The cerebrospinal fluid was examined in 4 cases in this series. No abnormalities were noted in the chemical composition nor in the cytology.

SECTION VI.

A. THE LIVER IN RHEUMATOID ARTHRITIS.

Disturbances of liver function have been recorded in rheumatoid arthritis (BECKMAN, 1945), but autopsy examinations of the liver have revealed only the common degenerative changes encountered in many infections and toxaemias.

CARTER and MacLAGAN (1946) noted "some observations on liver function tests in diseases not primarily hepatic". They employed the colloidal gold test and the thymol turbidity test. They regarded the normal limits of the thymol turbidity test as 0 - 4 units, and stated that normal serum gave a negative result (recorded as 0) with the colloidal gold test. Among the cases examined was a series of 30 patients with rheumatoid arthritis. They found that the colloidal gold test was "positive" in 28 out of the 30 cases while the thymol turbidity test was much less sensitive, being "positive" in only 13 of these 30 cases. They stressed the wide discrepancy between the result of the 2 tests in this series of cases. Urobilinuria was absent in 18 out of 19 cases examined, and the authors suggested that the high proportion of positive results was not specifically related to liver pathology. They suggested that an antibody associated with the serum gamma-globulin fraction might be responsible

for ...../

for the flocculating power of patients with rheumatoid arthritis. FRASER (1948) found that the colloidal gold test was "positive" in 61 per cent of a series of 133 cases of rheumatoid arthritis.

Liver function tests (serum proteins, colloidal gold, thymol turbidity and thymol flocculation tests) were performed in 52 cases of rheumatoid arthritis. The serum proteins were estimated in 46 cases, and the colloidal gold test was performed in 40 cases, the thymol turbidity test in 47 cases and the thymol flocculation test in 26 cases. The results are shown in Table 15.

TABLE 15- RESULTS OF LIVER FUNCTION TESTS IN 52 CASES

Case	Duration	Serum Albumen	Serum Globulin	Total Protein	Thymol Turbidity	Colloidal Gold	Thymol Flocculation
1	6	4.0	2.6	6.6	1	-	-
2	6	4.4	2.8	7.2	1	1	1
3	8	3.9	1.9	5.8	3.5	-	-
4	1	3.9	3.3	7.2	2.5	5	-
5	5	4.1	1.8	5.9	2	3	-
6	43	4.6	2.7	7.5	7	5	4
7	3	4.4	2.8	7.2	5	5	4
8	4	2.6	3.6	6.2	-	-	-
9	2	3.6	4.1	7.7	11	4	4
10	5	3.5	2.7	6.2	-	-	-
13	2	4.5	1.9	6.4	1.5	-	-
15	9/12	2.7	4.9	7.6	9	4	-
16	7	3.9	5.0	8.9	2.5	5	-
17	3½	4.1	3.7	7.8	2.5	1	1
18	8½	4.5	2.4	6.9	2.5	1	1
20	8	4.1	3.5	7.6	1.5	1	-
21	8	3.2	4.2	7.4	2.5	4	3
25	1	-	-	-	2.5	1	1
26	45	4.5	1.7	6.2	1	1	-
27	5	4.3	2.2	6.5	1	-	-
28	1½	-	-	-	1	1	-
29	2	4.5	4.4	8.9	1.5	1	-
30	2	4.0	4.1	8.1	6	1	-
31	10	4.3	1.4	5.7	-	-	-
32	2	2.8	5.7	8.5	5.5	5	4
35	11	3.6	3.6	7.2	5	3	3
36	2	2.1	2.6	4.7	4	-	-
37	3	4.4	2.1	6.5	1	-	-
39	10	3.8	2.1	6.1	3.5	1	1
40	5	-	-	-	1.5	-	-
43	1	3.9	2.6	6.5	1.5	1	-

Continued overleaf...

TABLE 15- RESULTS OF LIVER FUNCTION TESTS IN 52 CASES

(continued)

Case	Duration	Serum Albumen	Serum Globulin	Total Protein	Thymol Turbidity	Colloidal Gold	Thymol Flocculation
44	9/12	3.5	2.4	5.9	1.5	1	1
45	9/12	3.3	3.5	6.8	5.5	3	4
46	30	3.7	2.6	6.3	3	4	2
47	3	-	-	-	5.5	1	1
48	1	3.7	3.0	6.7	1.5	1	-
49	14	4.5	2.0	6.5	3	4	3
50	19	4.1	2.3	6.4	1.5	1	-
51	12	3.6	3.0	6.6	2.5	1	1
54	6	4.7	3.0	7.7	2.5	1	1
55	16	4.0	2.8	6.8	4	2	1
56	4	3.8	3.3	7.1	1.5	-	-
57	17	4.2	2.3	6.5	1.5	2	1
58	8	-	-	-	1.5	2	-
61	3	4.3	2.8	7.1	1.5	1	1
62	8	4.9	3.1	8.0	7	5	3
64	20	3.9	2.9	6.8	2.5	4	3
65	9/12	3.8	3.0	6.8	3.5	4	2
66	1	-	-	-	-	2	-
67	11	3.7	4.0	7.7	5	5	1
69	7	4.4	3.0	7.4	-	-	-
70	12	3.3	3.2	6.5	5.5	4	5

DISCUSSION.

The total serum proteins was normal in the large majority of the cases but in 7 instances the serum albumen was less than 3.5 per cent, and in 11 instances the serum globulin was more than 3.5 per cent.

The thymol turbidity test was more than 3 units in 17 cases (and in 12 of these it was more than 4 units). It was less than 3 units in 30 cases.

The colloidal gold test was "positive" in each of the 40 cases in which it was performed. In 18 cases the result was "markedly positive" (3, 4 or 5); in 4 cases it was "positive" (2) and in 18 cases it was "weakly positive" (1).

The thymol flocculation test showed incomplete flocculation (1+) in 13 cases and complete flocculation in 13 cases.

.. ..

The results of these tests largely confirm the findings of CARTER and MacLAGAN (1946), and indicate that both the colloidal gold and the thymol turbidity tests are frequently "positive" in rheumatoid arthritis but that there was a wide discrepancy between the results

of the ...../

of the 2 tests in this disease. The colloidal gold was "positive" in all 40 cases and the thymol turbidity test was "positive" in only 12 out of 47 cases.

.. ..

These abnormal liver functions were not the result of crysotherapy as only 11 cases in the series of 52 cases examined had ever received gold injections.

B. GASTRO-INTESTINAL SYSTEM.

COMROE (1944) stated that achlorydria seldom occurs in rheumatoid arthritis. The Committee of the American Rheumatism Association noted the occurence of achlorydria in the disease but considered that the advanced ages of the patients may have been responsible for the achlorydria.

HARRISON,(1943) included the result of Fractional Test Meals performed in 14 cases of rheumatoid arthritis in his table. Five had achlorydria.

Fractional Test Meals were performed in 23 cases in this series (Table 16).

Table ...../

TABLE 16.

RESULTS OF FRACTIONAL TEST MEAL - 23 CASES.

Case	Result	Age
2	Normal	43
5	Hyperchlorydria	60
6	Hyperchlorydria	78
7	Normal	51
10	Hypochlorydria	51
13	Achlorydria	65
21	Normal	36
27	Hypochlorydria	17
29	Normal	46
36	Achlorydria	44
37	Achlorydria	62
45	Hypochlorydria	28
48	Hypochlorydria	32
50	Achlorydria	59
51	Hypochlorydria	44
52	Achlorydria	48
56	Normal	70
58	Normal	44
60	Normal	31
61	Achlorydria	69
63	Achlorydria	69
64	Achlorydria	61
69	Achlorydria	69

Nine...../

Nine of the 23 cases had histamine-fast achlorydria (39 per cent). However, it can be seen that the ages of the cases with achlorydria (65, 44, 62, 59, 48, 69, 69, 61, 60) were on the average higher than in the ages of the 7 cases with normal acidity (43, 51, 35, 48, 70, 44, 31). HARRISON (1943) observed that it has been shown that about 25 per cent of individuals "in the sixties" had achlorydria, and the high proportion of cases of achlorydria in these 23 cases may be largely due to the age incidence.

c. THE KIDNEY IN RHEUMATOID ARTHRITIS.

The kidneys are one of the sites which may be involved if amyloidosis develops as a complication of rheumatoid arthritis.

Apart from amyloidosis of the kidneys there are few reports of the renal abnormalities encountered in autopsies on cases of rheumatoid arthritis.

ROSENBERG, BAGGENSTOSS and HENCH (1943, 1944) stated that one of the surprising findings at autopsies on 30 cases of rheumatoid arthritis was the occurrence of a high incidence of microscopical renal lesions. They stated that glomerular endothelial proliferation was present in many cases and considered that the agent responsible for rheumatoid arthritis may have also been responsible for the "lowgrade glomerulitis".

BAYLES (1943b) BENNETT (1943) FINGERMAN and ANDRUS (1943) and YOUNG and SCHWEDEL (1944) noted renal lesions in some of their autopsied cases during their examination of the cardiovascular system. BAYLES (1943b) noted "nephritis" in one case; "chronic glomerularnephritis" in a second case; and "nephritis" in a third case during his examination of 23 cases. BENNETT (1943) stated that "nephritis" was

present ...../

present in 4 of the 48 autopsied cases. FINGERMAN and ANDRUS (1943) found no marked microscopic abnormalities of the kidneys but stated that 19 of the 61 cases had "granular pitted surfaces with adherent capsules". On histological examination, kidneys from 8 cases showed "glomerulitis with a moderate to a marked increase in endothelial nuclei"; most of the patients in this group had some sort of concomitant infection such as decubital ulcers, pneumonia or septicaemia, and 2 had "clinical signs of glomerulonephritis". YOUNG and SCHWEDEL (1944) described 3 cases in their series of 38 cases with "acute diffuse glomerulonephritis", "acute nephritis", and "diffuse nephritis" respectively.

The terminology used by these investigators is varied and it is not possible to reach any conclusion in regard to the frequency of true diffuse glomerulonephritis in their cases of rheumatoid arthritis.

If true glomerulonephritis is proved to be a common pathological feature in rheumatoid arthritis it would illustrate an interesting relationship to the visceral angeitides which commonly include arthritis and nephritis amongst their features.

Clinically, there is no special mention in the

literature...../

literature of any undue incidence of glomerulonephritis in rheumatoid arthritis. In fact, ROSENBERG, BAGGENSTOSS and HENCH commented on the paucity of clinical evidence of renal disease in rheumatoid arthritis (1944).

The blood urea was estimated in 21 cases in this series. It was less than 40 mg. per cent in 16 cases. In 3 elderly patients, aged 72, 66 and 77 the blood urea was 41, 41 and 46 mg. per cent respectively, and these figures would be accepted as within normal limits at these ages.

Abnormalities in renal function were noted in 2 cases. Case 36, a man aged 57, had rheumatoid arthritis for 2 years. The blood urea was 44 mg. per cent on admission and rose to 102 mg. per cent 6 months later. A massive albuminuria was constantly present and the urine constantly contained very numerous pus cells and organisms. The diagnosis was made of chronic suppurative pyelonephritis and was regarded as the cause of the azotaemia.

Case 39 had rheumatoid arthritis for 10 years. A massive albuminuria was detected on her admission to hospital 3 years ago and it is still present. The urine constantly contained numerous hyaline and granular casts; its daily specific gravity of the urine was not fixed. There was no hypertension and the blood urea was 38 mg. per cent. A chronic renal lesion

appeared...../

appeared to be present. The albuminuria was first observed after she had received crysotherapy several years ago, and it is possible that a toxic effect of the gold on the kidneys is the explanation of the renal lesion.

A few cases had slight albuminuria and scanty granular and hyaline casts but none of the 70 cases showed clinical signs of acute or chronic diffuse glomerulonephritis.

D. AMYLOIDOSIS IN RHEUMATOID ARTHRITIS.

1. Discussion.

With the exception of chronic suppurative conditions, tuberculosis, syphilis and multiple myelomatosis, rheumatoid arthritis is one of the commonest diseases leading to the development of amyloidosis. This has not always been recognised and, in 1935, e.g. PERLA and GROSS described the autopsy findings of amyloidosis of the kidneys, adrenals and liver in a case of "chronic polyarthritis". As the arthritis was not suppurative they regarded the case as one of "primary amyloidosis" without an obvious cause. The "chronic polyarthritis" had been present for 10 years and in reviewing the article it is apparent that they were dealing with a case of chronic rheumatoid arthritis complicated by amyloidosis.

TRASOFF, SCHNEEBERG and SCARF (1944) have reviewed the literature on the occurence of amyloidosis in rheumatoid arthritis in a masterly manner, and have discussed all aspects of the problem. They commented on the relative paucity of records of such cases in the literature they reviewed.

There...../

There is no satisfactory explanation for the occurrence of amyloidosis in chronic rheumatoid arthritis. Its occurrence has been attributed to the hyperglobulinaemia that sometimes occurs in certain chronic diseases (e.g. multiple myelomatosis) but the problem remains unsolved. In the case which was recorded by TRASOFF, SCHNEEBERG and SCARF (1944) there was no hyperglobulinaemia, and this has been noted by other workers too.

From their review of the literature TRASOFF, SCHNEEBERG and SCARF (1944) have noted that the cases of rheumatoid arthritis which develop amyloidosis are nearly always the severer cases. On the other hand, BECKMAN (1945) discussed a case of amyloidosis which developed in a non-progressive case of rheumatoid arthritis.

YEOMAN and WILSON (1947) described a case of rheumatoid arthritis which intermittent albuminuria in spite of the presence, at autopsy, of marked amyloidosis of the kidneys. They noted that the usual distribtuion of amyloidosis in cases of rheumatoid arthritis resembled the distribution of amyloidosis occurring in chronic suppurative conditions, etc. The amyloid is deposited in the kidneys, spleen liver and adrenals usually, and not in atypical

sites...../

sites such as tongue, cardiovascular system, smooth and striated muscle and other mesodermal tissues. Its distribution thus corresponds with that of "Secondary Amyloidosis" (REIMANN, KOUCKY and EKLUND, 1935).

TRASOFF, SCHNEEBERG and SCARF (1944) from a review of the literature came to the conclusion that "the development of amyloidosis in the course of rheumatoid arthritis is an unusual occurrence" and that "it immediately converts an ordinary benign disease into one with a high mortality".

The case they described proved to be the exception to the rule. The diagnosis of amyloidosis was made because of the development of splenomegaly, hepatomegaly, generalised oedema and albuminuria. The Congo Red test showed retention of 90 per cent, or more, of the dye on 3 separate occasions. Three years later there was no evidence of any of these abnormal clinical and chemical findings, and the joint deformities had "almost completely disappeared".

FINGERMAN and ANDRUS (1943) noted a high incidence of amyloid disease in their series of 61 autopsies. Amyloidosis was present in 13 cases (21 per cent). The spleen was most commonly involved and the kidneys, liver and adrenals were often affected. In 3 of these cases active pulmonary tuberculosis was present and this may have been the etiological

or ...../

or a contributory factor, in these particular cases.

REIMANN and EKLUND (1935) and SOLOMON (1943) have described cases of amyloidosis which developed after the treatment of the rheumatoid arthritis with repeated injections of vaccines. As there is definite experimental evidence of the development of amyloidosis in horses which were used for the production of various antisera, both these authors considered the possibility that the amyloidosis in their cases was due to the vaccine therapy. They both favoured this possibility but it is obviously not possible to reach a definite conclusion as rheumatoid arthritis, without vaccine therapy, is such a well known cause of amyloidosis.

2. Congo Red Test.

A review of the literature indicates that the presence of amyloidosis in cases of rheumatoid arthritis has usually been a post-mortem observation. In some instances the diagnosis was suspected clinically and Congo Red Tests were performed during the lifetime of the patients.

It was considered that the performing of Congo Red Tests in a series of cases of the disease might yield information of value and of interest. The test was performed in 15 cases and the results tabulated in Table 17.

TABLE 17 ...../

TABLE 17 :

RESULTS OF CONGO RED TESTS.	
Cases 15	Per cent of the dye in the serum after one hour.
6	61
7	80
10	60
13	54
16	70
21	46
26	58
30	52
37	53
39	68
50	80
56	65
61	73
64	60
69	70

The cases selected for the test were mainly the advanced cases of the disease. Of the 15 cases 9 were from the Conradie Home, and 3 of the remaining cases were of 19, 43 and 45 years duration (Cases 50, 6 and 26).

Case 21 had the lowest per cent of the dye remaining in the serum after one hour, i.e., 46 per cent. This is equivalent to stating that there was "54 per cent retention of the dye".

There is not universal agreement on the interpretation to be placed on the results of Congo Red Tests. In former years it was often thought that the diagnosis of amyloidosis could be confirmed if 60 per cent or more of the dye disappeared from the blood after one hour, i.e. if there was more than "60 per cent retention of the dye". However, LIPSTEIN (1938) carefully correlated the results of Congo Red Tests with the later findings at autopsy, and concluded that "in the presence of amyloidosis the Congo Red absorption ranged from 90 to 100 per cent", in the majority of the cases of proved amyloidosis. He found, too, that in the absence of amyloidosis the dye absorption varied between 10 and 75 per cent in the vast majority of the cases. The conclusion is that amyloidosis should not be diagnosed unless there is 90 per cent (or more) retention of the dye.

In...../

In the above series of 15 cases the highest degree of retention which occurred was 54 per cent. (case 21). Therefore, irrespective of whether 60 per cent or 90 per cent retention is regarded as the diagnostic level for amyloidosis, none of the 15 cases in this series yielded results which could be interpreted as diagnostic for amyloidosis.

Unfortunately the problem is not quite so simple. LIPSTEIN (1938) noted 2 exceptions to the general rule: (i) a few cases of proved amyloidosis (at autopsy) had retention values of only 35 per cent; and (ii) a few cases with retention values of 90, 95 and even 100 per cent did not have amyloidosis at autopsy! The first set of exceptions is particularly interesting as it indicates that amyloidosis may be present even though the Congo Red Test does not indicate 90 per cent (or more) retention of the dye.

The final conclusion, thus, is that while it has not been possible to prove the presence of amyloidosis in these advanced cases of rheumatoid arthritis, it has also not been possible to exclude the presence of amyloidosis with any certainty.

.. ..

Recently...../

Recently SELIKOFF (1947) has suggested a further modification of the Benhold's Congo Red Test. He stated that the test should be repeated twice, consecutively, and that the diagnosos of amyloid should only be made if there was "complete or nearly complete absorption" of the dye on both occasions. If the test was performed in this way he considered that it would not give any "false positives" for amyloidosis.

3. Amyloid in Subcutaneous Nodules.

Sections of 11 subcutaneous nodules were stained with Congo Red to determine the presence or absence of amyloid deposition.

The nodules which were stained were mainly larger nodules containing many large areas of necrosis.

In some parts of several of the sections the tissues were stained a faint pink colour, but no definite deposition of amyloid could be demonstrated in any of the cases.

There was thus no evidence of amyloid deposition in the subcutaneous nodules according to the results of the Congo Red stains. The nodules were not stained with methyl violet or with gentian violet.

SECTION VII.

CONCLUSIONS.

A. GENERAL SUMMARY.

Subcutaneous nodules were encountered in approximately 29 per cent of the series of 70 cases with rheumatoid arthritis. Of the 20 cases from the "Conradie Home" a relatively large number (8) had nodules: if these 20 cases are excluded, the incidence of the occurrence of nodules in the remaining 50 cases would be 24 per cent. These nodules are thus a characteristic finding, if sought for, in a large number of cases of chronic rheumatoid arthritis.

A wide variety of visceral lesions were noted in the series. They included skin and nail lesions (pigmentation, psoriasis, onycholysis and onychogryphosis); iritis; cardiac valvular lesions; splenomegaly and lymphadenopathy. Achlorhydria was often present and the liver function tests were disturbed in a high percentage of cases. "Nodular myositis" was found in approximately 40 per cent of deltoid muscle biopsies in a series of 34 cases. There was no evidence clinically of glomerulo-nephritis and the presence of amyloidosis could not be detected in any of the cases.

These results were carefully studied in order to determine whether or not there was any

tendency ...../

tendency for certain of these findings to occur grouped together. The conclusion was reached that any of these features alone, or any combination might occur, and that there was no special tendency for them to occur in particular associations. A few cases showed numerous features, e.g. Case 2 had a subcutaneous nodule, valvular heart disease and iritis, but most of the cases had only one or two of the findings enumerated.

There was no apparent relationship between the cases with subcutaneous nodules and those with valvular heart disease. Only one of the 20 cases with nodules had clinical evidence of valvular heart disease.

Similarly there was no apparent relationship between the occurrence of nodules and the finding of "positive" muscle biopsies.

B. DETAILED CONCLUSIONS.

1. Seventy cases of chronic rheumatoid arthritis were examined and their clinical features were noted.

(a) The clinical features corresponded closely with the descriptions of the disease given in English and in American literature, and no differences attributable to local climatic conditions were noted.

(b) There were no significant differences between the clinical features of the European and Non-European cases. Facial pigmentation was commoner in the Non-European cases but this was probably of no significance.

(c) The terminal interphalangeal joints were affected in 14 of the 70 cases. In 6 of these 14 cases there was radiological confirmation of this involvement, and illustrations were shown of several of these cases. This relatively high incidence was not surprising in view of the evidence in the literature that the terminal joints may be involved at autopsy examination, but it was not in conformity with the hitherto accepted view that the joints are practically never affected in rheumatoid arthritis.

It was...../

It was noted that the majority of the cases with involvement of the terminal joints were advanced cases which had the disease for long periods.

(d) The sedimentation rates were estimated in nearly all the cases in this series. It was noted that the rates remained elevated in some cases which were, clinically, completely or almost completely "burnt out". This indicated that "activity" was sometimes detectable in rheumatoid arthritis even after the disease had been present for many years and had reached the terminal stage of painless deformity and ankylosis.

(e) A typical case of a condition which is sometimes known as "Arthritis Mutilans" was described. The clinical and radiological features of the case corresponded closely with descriptions of similar cases in the literature. However several other cases were seen in this series which had clinical and radiological features intermediate in severity between cases of "Arthritis Mutilans" and advanced cases of chronic rheumatoid arthritis. The features of several such cases were illustrated. One of these cases had mutilating changes confined to a

thumb ...../

thumb similar to those described in other cases of "Arthritis Mutilans" reported in the literature. It was therefore suggested that "Arthritis Mutilans" is not a distinctive entity but represents cases with the grossest and most deforming sequelae of chronic rheumatoid arthritis. The cause of the extensive mutilation appears to be the marked or complete destruction of the joints and the epiphyseal ends of the adjacent bones with replacement by fibrous or fatty tissue.

(f) A case of rheumatoid arthritis with psoriasis was described. It is interesting that a few cases of psoriasis are nearly always found when large series of rheumatoid arthritis are examined. "Psoriatic Arthritis" probably represents a true association and not a mere coincidence of the 2 diseases.

(g) Onychogryphosis was noted in one case. It developed within a few months after the onset of the arthritis.

(h) Iritis occurred in 4 cases. In 2 of these cases it occurred several years before the onset of the arthritis and recurred cyclically each year in a manner suggestive of an "allergic" disorder.

(i) ...../

(i) Splenomegaly was noted in 7 cases, lymphadenopathy in 20 cases (excluding cases with enlargement of only the inguinal or cervical lymph glands) and leucopenia in 5 cases. These 3 features occurred either singly or in various combinations. One case of "Still's Disease" was noted in a 9-year old girl and one case of "Felty's Syndrome" was noted in a 52-year old woman.

There is a definite tendency noted in the literature to cease using the terms "Still's Disease" and "Felty's Syndrome" as they are not regarded as specific entities. "Still's Disease" is juvenile rheumatoid arthritis and the lymphadenopathy and splenomegaly which are commonly present may also occur, though perhaps less frequently, in adult cases. "Felty's Syndrome" has, in some instances, resulted from the simultaneous occurrence of another disease (e.g. "Banti's Syndrome") in cases of rheumatoid arthritis; in other instances the splenomegaly was due to amyloidosis and in other cases the "Syndrome" resulted from the combination of several features, any of which is known to occur singly in rheumatoid arthritis.

(j) ...../

(j) Two cases with pulmonary tuberculosis were detected in the examination of the series of cases. This incidence is not considered to be higher than that which might occur by coincidence in routine radiological examinations of the chest, and it does not furnish evidence in support of the concept of "Tuberculous Rheumatism".

2. SUBCUTANEOUS NODULES.

(a) Twenty of the 70 cases had either one nodule or multiple nodules. The incidence of the occurrence of nodules in this series was therefore approximately 29 per cent. This incidence is slightly higher than that which has been previously recorded in the literature. If the 20 advanced cases from the chronic sick home are excluded, the incidence would be 24 per cent.

(b) Eight of the 20 cases had one nodule and 12 cases had 2 or more nodules. A total of 99 nodules was noted in 20 cases.

(c) The nodules were situated most commonly over the olecranon process, or along the ulnar border of the forearm 1-2 inches distal to the tip of the olecranon. Forty-three of the 99

nodules...../

nodules occurred at one of these 2 sites and this finding confirmed the reported frequency with which the nodules occurred at the elbows.

(d) The nodules varied in size, consistency, relationships and colour. The nodules situated over the olecranon process appeared in some cases to have originated in the olecranon bursa; these nodules often attained great sizes and were often lobulated.

(e) The role of trauma in the production of the nodules was noted. The liability to develop nodules was provided by the presence of the disease, and it appeared from the histories and the examinations of the cases that trauma very often played a part in the production and localization of the nodules. The role of trauma was indicated by several brief case-records and by illustrations.

(f) The significance of the appearance of nodules in early cases and their effect on the prognosis of the arthritis has not yet been determined or proved.

The appearance of nodules in the more advanced and deformed cases may be largely the result of the deformities. Thus, while

it is ...../

it is true that the incidence of nodules is highest in the most crippled and deformed cases, the explanation may be that the nodules are the result of the arthritic havoc. Some severe cases were encountered without nodules and, on the other hand, some milder cases did have nodules.

(g) The macroscopic appearances of several of the nodules after biopsy were described and illustrated.

(h) The histological appearances of 19 nodules were described and illustrated in detail.

(i) Sixteen of the nodules had the characteristic histological appearances which have been described in the subcutaneous nodules of rheumatoid arthritis. They contained one focus, or several foci, consisting of a necrotic zone, an intermediate cellular zone of radially-arranged mononuclear cells and a peripheral zone of fibrous tissue. Perivascular infiltration of small blood vessels was noted in some nodules.

(j) One nodule consisted only of cellular fibrous tissue and the section did not show the presence of any of the characteristic foci with necrosis.

(k) One nodule contained areas of

calcification...../

calcification. It was the hardest and the most mobile nodule encountered in the series. The illustrations indicated that the calcified areas appeared to correspond in shape and in size with the necrotic zones noted in the centre of the foci in the characteristic nodules.

(1) The problem of lipoid deposition in the subcutaneous nodules was the subject of specially careful and detailed examination. One nodule consisted mainly of cholesterol and lipoid and its macroscopical and microscopical appearances were illustrated in detail. The presence of large amounts of lipoid in the necrotic areas was demonstrated in 6 out of 9 additional nodules stained with Scarlet Red. It was therefore suggested that the deposition of lipoid was not at all uncommon in the nodules of rheumatoid arthritis. The presence of cholesterol crystals and of cholesterol "clefts" had been recorded previously in the literature and this investigation revealed the presence of a fairly high incidence of lipoid in the nodules after the use of special stains.

The literature on "nodules of rheumatoid arthritis type with lipoid deposition" is small and was...../

and was carefully reviewed. It was suggested that the nodules described by various authors were not distinct entities but were merely different histological end-results of a process with a common etiology and pathogenesis.

It was also noted that lipoid deposition in the nodules was not related to, nor dependent on, the level of the serum cholesterol.

(m) The relationship to the subcutaneous nodules of rheumatic fever was briefly mentioned.

(n) The clinical features of the nodules were contrasted with those of tophi in cases of gout. The common site of occurrence of the nodules of rheumatoid arthritis, viz. along the ulnar border, was not pathognomonic as 2 cases of gout had subcutaneous tophi at this site.

(o) The striking resemblance between the clinical features of the nodules of rheumatoid arthritis and of xanthoma tuberosum et planum was discussed and fully illustrated.

3. The cardiovascular system was investigated by means of clinical, electrocardiographic, radiological and phonocardiographic examinations. In spite of the extensive investigations the presence of valvular heart disease could not be demonstrated in more than 4 of the 70 cases.

The ...../

The etiology of the valvular disease was "rheumatic" in 3 cases and almost certainly "rheumatic" in the fourth case.

Clinical and electrocardiographic and radiological abnormalities were noted in other cases in the series, but the abnormalities were either insignificant or attributable to coincident hypertension or arteriosclerosis.

The use of the phonocardiogram did not result in the detection of any diastolic murmurs which were not audible on clinical examination.

From a review of the literature it appears that about 40 per cent of cases of chronic rheumatoid arthritis have rheumatic valvular disease at autopsy, yet on clinical examination during the lifetime of the cases, the valvular disease has seldom been detected. In this series, there was a low, but probably significant, incidence of valvular heart disease in about 6 per cent of the cases. There is no clear explanation available to reconcile the discrepancy between the pathological and the clinical findings in the cardiovascular system.

4. ...../

4. The literature on the neuromuscular system in rheumatoid arthritis was reviewed.

(a) In a series of deltoid muscle biopsies performed in 34 cases of rheumatoid arthritis one nodule, or multiple nodules, were found in the endomysium or in the perimysium in 14 cases. The histological appearances of the "positive" muscle sections closely resembled the descriptions of "nodular polymyositis" given in the literature and several illustrations were shown.

(b) The incidence of "positive" biopsies was lower than that noted by most investigators but paralleled the incidence recorded by a few other workers. They occurred in "active" and "burnt-out" cases.

(c) The nodules were detected with great facility in the muscles on histological examination of the sections. In some cases they were sufficiently large to be visible on naked eye examination.

(d) In an examination of the muscles of a small "control" series of 20 cases by biopsy or at autopsy, similar inflammatory nodules were found in only one case - a case of gout.

(e) ...../

(e) The histological appearances of the inflammatory nodules present in the case of gout showed certain resemblances to the nodules described and illustrated in the muscle biopsies in rheumatoid arthritis, but certain additional features rendered the differentiation easy. A second case of gout did not show similar muscle lesions but it is suggested that biopsies of muscle and subcutaneous tissue in cases of suspected gout before the appearance of tophi might perhaps reveal information of diagnostic value.

(f) Muscle examinations in 2 cases of polyarteritis nodosa showed the characteristic vascular lesions encountered in the disease.

(g) In the review of the literature it was noted that one set of investigators reported a fairly high incidence (26.2 per cent) of occurrence of "nodular myositis" in a collection of 450 miscellaneous cases at autopsy. Investigations on a correspondingly large scale are necessary to confirm or to refute their claims. If their findings are

confirmed...../

confirmed, and there is no special reason for doubting the accuracy of their observations, it would indicate that "nodular myositis" is a comparatively common condition in a wide variety of diseases and that it has no diagnostic value in cases of rheumatoid arthritis.

The number of control cases in this review was too small to enable useful conclusions to be drawn, but the results were in conformity with the findings noted by most investigators in the examination of muscle by biopsy or at autopsy in "control" cases.

(h) The histological findings in the muscles and in the peripheral nerves in cases of rheumatoid arthritis may be the explanation of the prominent neuromuscular clinical features often present in the disease.

5. The results of certain liver function tests were found to be often abnormal. An inversion of the serum albumen/globulin ratio was commonly encountered, and several cases showed hyperglobulinaemia. The colloidal gold reaction and the thymol turbidity test (especially the former) were "positive" in a large number of cases.

6. ...../

6. Nine of 23 cases examined had histamine-fast achlorhydria. This high incidence may have been largely or entirely due to the age incidence of the cases examined.

7. Two cases were noted which had evidence of chronic renal disease. One case had chronic suppurative pyelonephritis and the second case developed the signs of renal disease after cryotherapy. There was no clinical evidence of diffuse glomerulonephritis in the series of cases examined.

8. Amyloidosis has often been recorded in the literature in cases of chronic rheumatoid arthritis. Its presence could not be proved by the Congo Red test which was performed in 15 cases.

   There was no evidence of amyloid deposition in any of the 11 subcutaneous nodules which were specially stained and examined.

9. A wide variety of "visceral lesions" were encountered in this series of 70 cases of rheumatoid arthritis, but there was no tendency for any of them to occur in particular associations with each other.

INDEX OF CASES STUDIED.

RHEUMATOID ARTHRITIS.

Number	Name	Sex	Age
1	A. Ab.	F	55
2	D. A.	M	43
3	A. Av.	F	57
4	A. B.	F	47
5	C. B.	M	60
6	I. B.	M	78
7	W. B.	M	51
8	S. B.	F	73
9	T. B.	M	53
10	L. B.	F	51
11	F. B.	F	62
12	K. C.	F	51
13	W. C.	M	65
14	S. C.	F	63
15	J. C.	F	41
16	F. D.	M	34
17	M. Da.	F	49
18	M. De.	F	35

19...../

RHEUMATOID ARTHRITIS.

Number	Name	Sex	Age
19	R. P.	F	35
20	J. D.	M	46
21	C. D.	M	35
22	R. E.	M	24
23	S. G.	F	34
24	R. G.	M	17
25	E. H.	F	60
26	C. K.	F	53
27	L. H.	F	17
28	F. J.	F	41
29	F. J.	F	48
30	J. K.	M	48
31	F. K.	M	42
32	S. K.	M	39
33	J. K.	M	21
34	S. L.	F	36
35	E. L.	F	44
36	N. Le.	M	53
37	M. L.	F	62
38	I. L.	M	45
39	Z. L.	F	35

40...../

RHEUMATOID ARTHRITIS.

Number	Name	Sex	Age
40	M. Li.	F	62
41	C. L.	F	61
42	V. L.	M	15
43	B. M.	F	17
44	A. Mil.	M	43
45	A. Mit.	F	25
46	E. M.	F	72
47	J. O.	F	49
48	E. P.	M	32
49	C. R.	F	39
50	W. R.	F	59
51	T. R.	M	44
52	M. S.	F	48
53	J. Se.	F	66
54	F. S.	F	39
55	J. Sh.	F	46
56	J. Sm.	F	70
57	C. S.	F.	44
58	R. S.	F	66
59	I. S.	F	9

60...../

RHEUMATOID ARTHRITIS.

Number	Name	Sex	Age
60	W. T.	M	31
61	J. U.	F	69
62	M. Val.	F	52
63	M. Vam.	F	69
64	J. Va.	F	61
65	J. Ve.	M	60
66	C. W.	F	29
67	L. W.	F	77
68	E. W.	F	62
69	M. W.	F	60
70	Z. Z.	F	40

INDEX OF CASES STUDIED.

ANKYLOSING SPONDYLITIS.

Number	Name	Sex	Age
71	B.D.	M	30
72	J.H.	M	41
73	S.B.	M	36
74	L.S.	M	23
75	M.J.	M	42
76	M.L.	M	55
77	S.A.	M	30

INDEX OF CASES STUDIED.

G O U T.

Number	Name	Sex	Age
78	S.B.	M	45
79	J.H.	M	65
80	F.B.	M	56
81	A.M.	M	50
82	J.M.	M	44
83	S.G.	M	43
84	J.W.	M	66
85	A.T.	M	43
86	V.R.	M	63
87	W.B.	M	49
88	J.R.	M	51

XANTHOMA TUBEROSUM ET PLANUM.

89	E.P.	F	32

ACKNOWLEDGEMENTS.

I am greatly indebted to Prof. F. Forman for his valuable interest, help and criticism in this investigation.

I also wish to thank the Honorary Physicians of the Groote Schuur Hospital, Cape Town, and the Medical Staff of the Conradie Home, Cape Town, for permission to investigate the cases under their care. I am particularly grateful to Dr. P.W.J. Keet for his helpful assistance at the Arthritic Clinic, Groote Schuur Hospital.

My thanks are also due to the following persons for the assistance they have unstintingly given me:

To: Prof. B.J. Ryrie and to Prof. M. van den Ende for assistance and facilities in the Department of Pathology, University of Cape Town;

Dr. G. Selzer for valuable assistance in the histological examinations;

Prof. R.H. Goetz for allowing me to use the phonocardiogram;

Dr. G.C. Linder for the facilities afforded by his Department;

Mr. E.J. Duncan for assistance with the chemical investigations;

Mr. W. Taylor for valuable help with the histological preparations;

The staff of the Radiological Department, Groote Schuur Hospital;

Mr. G.C. McManus for photographs and microphotographs;

Mr. J. de Villiers for some of the clinical photographs;

Miss E. Scholtz for technical assistance;

The Staff of the Medical Library, University of Cape Town;

Dr. Spohr and the Staff of the Jagger Library, Photostat Department;

Those who have assisted with typing the thesis;

The resident medical, nursing and administrative staff of the Groote Schuur Hospital, and particularly to the nursing staff in the Casualty Department for their untiring aid in this investigation; and to

The housemen and medical students who have assisted me while performing the biopsies.

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