THE NATURE OF THE SO-CALLED RHEUMATOID ARTHRITIS AND OSTEO-ARTHRITIS.

SUMMARY OF

AN INVESTIGATION INTO THE PATHOLOGICAL CHANGES, WITH
A PLEA FOR A SCIENTIFIC CLASSIFICATION.*

(With Special Plate.)

BY

A. G. TIMBRELL FISHER, M.C., F.R.C.S.ENG.,

ASSISTANT IN THE SURGICAL UNIT, UNIVERSITY COLLEGE HOSPITAL;
SURGEON WITH CHARGE OF OUT-PATIENTS, SEAMEN'S (DREADNOUGHT)
HOSPITAL, GREENWICH.

THE chronic forms of arthritis known in this country by the somewhat unscientific names "rheumatoid arthritis" and "osteo-arthritis" are among the commonest of all human ailments, and probably cause a greater loss of productive energy to the community than disease of any other system. It is true that the disease rarely, if ever, causes the death of the patient, but it often occurs in the comparatively young and active, to whom the resulting cripple-ness is a grave hardship. It is proposed in this paper to resist the temptation to discuss clinical aspects and treatment, and to review briefly certain aspects of the problem.

A. UNDERLYING REASONS FOR THE PRESENT STATE OF THE ARTHRITIC PROBLEM.

1. Ignorance of the Physiology of the Articulations.

It is a striking fact that until quite recently our ignorance of some of the most elementary facts concerning the articular cartilage and the functions of the synovial membranes and fluid was almost mediaeval. Claude Bernard wrote more than half a century ago with regard to the synovial fluid: "les données physiologiques sur ce liquide sont a peu près nulles: le siège anatomique de sa sécrétion est lui-même très peu connu." It is somewhat of a reproach that these words are well-nigh as true to-day as when written. Even otherwise exhaustive treatises on physiology either ignore the subject altogether or dismiss it in a few lines as one of minor importance. My own halting and imperfect efforts in this realm will be briefly touched upon below.

2. Ignorance of Normal Intimate Histological Structure.

There exists great variance of opinion concerning the histological structure of articular cartilage and synovial membrane. With regard to the former, some hold that a perichondrium is present over the whole surface, others that it is present at the periphery only; while another school, following Ogston, hold that the superficial cells are in reality degenerate, and are in process of being cast off into the joint. With regard to the synovial membrane, hardly any two authorities agree as to the nature of the cells with which it is lined. In regard to its connexions, Schafer states "they are not connected with the lymphatic system;" but by injecting colloidal silver solution into the knee-joint of a living animal I was able to show that absorption by the lymphatics definitely occurs.

When faced with such multiplicity of views it would appear sufficiently obvious that the course to adopt is not to argue but to look and see. This is the method I adopted, and what I saw has been described by me in a recent Hunterian Lecture upon osteo-arthritis. Some of the main points will be briefly enumerated below.

3. Ignorance of the True Nature of the Pathological Changes.

It is clear that before we can hope to treat any disease on rational lines we must have a clear conception of its essential nature.

At the outset we are faced with contradictory views. For instance, Goldthwait christened the two groups, which we in this country usually call rheumatoid arthritis and osteo-arthritis, as atrophic and hypertrophic arthritis re-

spectively. Nichols and Richardson, however, classify them into proliferative and degenerative arthritis. Thus the condition that we know as osteo-arthritis is interpreted by the former as a process of hypertrophy and by the latter as a degenerative process. Some may say, "This is very interesting, but how does it help the unfortunate sufferer?" I would reply that it is of fundamental importance in prognosis and treatment. If we accept the view that the disease is some form of degeneration having an obscure relation to old age, it is difficult to see how treatment can be of any avail or how the disease can be arrested. If, however, we accept the view that the disease is inflammatory in nature, it is clear that the disease assumes an entirely different complexion, and that we should not leave a stone unturned until we have discovered the source of the toxic substances that bring about these inflammatory changes. Moreover, like other inflammatory processes, they may come to a natural termination. Instead of a depressing policy of *laissez-faire*, we adopt a more active and cheerful outlook. I have known individuals who have been labelled "senile" arthritis of the hip converted from lives of painful crippledness to an active and comparatively painless existence. I propose to give a short description below of my conception of the nature of the changes.

4. A Confusing Nomenclature.

One of the commonest mistakes in this connexion lies in the investigator endeavouring to form a primary classification according to his conception of the nature of the pathological changes. Owing to the diversity of the latter confusion is bound to ensue. Another common error lies in mixing anatomical, clinical, and pathological subdivisions in the same classification. A good example of this lies in the terms "osteo-arthritis" and "rheumatoid arthritis." The former name is given owing to the supposed site of the principal changes, and is therefore anatomical. The latter term is a pseudo-clinical term in which the disease is compared, in terms reminiscent of the humoral pathology, to yet another disease, the etiology of which is still unsettled.

5. Lack of Co-operation between Physician, Surgeon, and Pathologist.

Specialism has its advantages, but we should never lose sight of its drawbacks and dangers. The policy followed at present is to divide many diseases into more or less arbitrary stages—the domain of the physician and surgeon respectively. Such divisions are obviously illogical and unnatural, and are among the most serious impediments to progress with which we are faced. We see the same lack of co-operation between physician and surgeon in the treatment of such conditions as gastric and duodenal ulcer. If we are to have specialists, let us have those who will make a thorough study of a system or organ and be responsible for the treatment of its disorders from beginning to end, whether operative or non-operative.

The surgeon's share consists very largely in dealing with the failures of medical treatment. The last twenty years have seen a great development of elaborate surgical technique; but I believe and trust that before the present century terminates we shall see a more healthy co-operation between physician and surgeon in the direction of the prevention of those advanced states that at present demand operation.

Sir Robert Jones has with great courage frequently protested against the existing lack of co-operation, and, thanks largely to his efforts, there has undoubtedly been improvement. It is unfortunately still only too common to meet with gross deformities which should never have been allowed to occur; and, on the other hand, for individuals to endure unnecessary pain and suffering because the physician has not acquainted himself with the possibilities of surgical measures in overcoming deformity or in restoring movement to the stiff joint. At the special Ministry of Pensions clinic at Orpington such co-operation exists, and the results, which have been most gratifying, lead one to believe that an extension of such clinics in civil life would be of great advantage.

* The expenses of this research were defrayed by the Medical Research Council, to whom my thanks are due.

B. THE ESSENTIAL NATURE OF THE SO-CALLED RHEUMATOID ARTHRITIS AND OSTEO-ARTHRITIS.

It is not my intention to describe in detail the pathological changes, since those occurring in osteo-arthritis have been described in detail by me elsewhere,¹ and the changes in rheumatoid arthritis have been described by many competent observers, particularly Nichols and Richardson and Strangeways. We have already seen that the pathological processes have received interpretations of an extraordinarily varied nature. Hence I propose to discuss shortly the true nature of the changes in the common types of chronic arthritis.

In the first pathological type, as Virchow pointed out, the disease commences in the central area of the articular cartilage and is associated with early "lippling" of the articular margins, although in rare cases this is absent. The synovial membrane is involved comparatively late, and never to the same degree as in the second type. This type of arthritis is known in this country by the name "osteo-arthritis." The well marked bony thickening with only slight changes in the synovial membrane and absence of "spindle-shaped" appearance of the joint, together with the usual moderate severity of the symptoms, form a well marked clinical picture. The earlier changes are very commonly seen *post mortem* in the joints of those who have passed the meridian of life.

In the second pathological type the process commences and remains more marked in the synovial membrane, and the articular cartilage is often, but not necessarily, invaded from the periphery. The formation of chondro-osteophytes, producing "lippling," is occasionally seen in the more chronic stages of the disease, but, as a rule, to a lesser degree and at a later stage than in osteo-arthritis. Pain and muscular spasm are more marked in this type and contracture deformity is common in neglected cases. This type of arthritis is known in this country by the name "rheumatoid arthritis."

In the third pathological type the process appears to start simultaneously in the synovial membrane and articular cartilage, and the change advances *pari passu*. Although borderline cases sometimes occur, usually there is not much difficulty in determining with which type we are dealing. It is clear that both pathologically and clinically these types, particularly the first two, have well marked distinguishing features.

TYPE 1.—Chronic Arthritis in which the Disease Commences in the Articular Cartilage (Osteo-arthritis).

The first departure from the normal consists, to the naked eye, in an alteration in colour of the surface of the central area of articular cartilage, which loses its normal bluish-white translucent appearance, and becomes more opaque and of a yellowish hue. Microscopically there is an alteration in the staining reaction of the matrix; for instance, with eosin the superficies stains very faintly compared with the deeper layer of the cartilage. There is at this stage no alteration in the cartilage cells. At a slightly later stage the so-called "fibrillation" of the matrix occurs at the surface of the central articular area. In a sense the term "fibrillation" is a misnomer, as there is no formation of true connective tissue fibre, but a mere splitting of the matrix. This appearance of fibrillation, as I have endeavoured to point out, is due to the peculiar structure of the matrix. If articular cartilage be steeped in brine for several days it will be seen that the matrix is arranged in alternating lamellae which lie horizontally in the superficial layers, form an irregular network in the intermediate zone, and constitute a palisade of vertical strata in the deeper layer. Histological examination shows that these alternate layers are formed by the more collagenous and the more mucinous elements of the matrix respectively. I believe that articular cartilage is nourished by lymph which percolates along these tracks, particularly the softer, more mucinous. I have little doubt also that the fibrillation is often due to the solution of the more mucinous tracks by toxic substances contained in the synovial fluid, whereby the more resistant collagenous elements remain as the so-called "fibres."

Now let us glance at the behaviour of the cartilage cells

at this early stage. Occasionally the cells at the extreme surface undergo degenerative changes. The most striking fact, however, is that in most cases the cells exhibit no sign of diminished vitality, and very often groups of actively proliferating cells may be seen. It is very striking, even in advanced cases, to see the "fibres" containing groups of healthy proliferating cartilage cells. A still more important point is that the most active proliferation occurs at the margins of the clefts in the matrix. This viability and active proliferation of the cartilage cells appears to me to be the very antithesis of an atrophic or degenerative process, at any rate as far as the cells are concerned. To me it seems fairly evident that the cells proliferate in response to irritation. We thus see that, as far as the central area of the articular cartilage is concerned, the change consists in a degenerative process in the cartilage matrix with proliferation of the cellular elements.

Shortly afterwards, or coincident with the above changes, the well known "lippling" of the articular margin occurs. This is caused by proliferation of the lateral part of the articular cartilage and of the underlying bone. As there is actual formation of new bone and cartilage cells, the term "hypertrophy" is a misnomer; but to regard the process as a pure degeneration is absurd. Later the cartilage on the surface of this new formation may undergo the same changes that we have seen to occur in the central area. As the cartilage disappears the subjacent bone becomes sclerosed from compensatory new bone formation. The deeper layer of articular cartilage is also invaded by vascular inroads of connective tissue which form new bone. The surface may thus be rendered hummocky—the epia-articular ecchondroses of Shattock (Fig. 1). The subjacent cancellous spaces are often of unusually open texture, due to a process of rarefying osteitis, and occasionally cyst-like spaces are in evidence. Some of these, I believe, may be due to cystic degeneration of islands of articular cartilage which have become isolated by the advancing tide of new bone formation.

Changes in the Synovial Membranes and Capsule.

For a considerable period no obvious changes may be seen in the synovial membrane, but eventually the portion of the membrane nearest to the articular margin becomes more villous. There is a hyperplasia of all its elements with occasional areas of small-cell infiltration, but the latter are rare compared with the second type, in which they are a prominent feature. Newly formed blood vessels are conspicuous, and show no evidence of arterio-sclerosis at this stage (Fig. 2).

During this stage of increased vascularity there is sometimes a development of adipose tissue, cartilage, or bone in the synovial membrane, but never to the same extent as in the second type. This increased vascularity and cellular proliferation strongly negative the primarily degenerative or atrophic view of the disease. The fact that the synovial fluid is usually not deficient in nutritive qualities is shown not only by my analyses, but by the fact that synovial chondromata and periarticular chondro-osteophytes may become detached and continue their growth while free in the joint. In the later stages the membrane and capsule may undergo sclerosis (Fig. 3); and with Hoffa and Wollenberg I have observed the occasional presence of areas of hyaline degeneration. Arterio-sclerotic changes may be seen in certain of the vessels of the synovial membrane, yet it is clear that these vascular changes advance *pari passu* with the changes in the membrane. It is also clear that they are not of etiological importance, but are coincident, and, like the changes in the membrane, inflammatory rather than degenerative.

Dr. Geoffrey Evans, in his recent investigations into the nature of arterio-sclerosis with special reference to its relation to chronic renal disease, has brought forward evidence that the latter is usually inflammatory in nature, as is also the coexistent arterio-sclerosis—that the latter is not of etiological import, but that both conditions are probably due to the same cause. The author and Dr. Evans have arrived at similar conclusions concerning the etiological importance of arterio-sclerosis through different avenues of approach.

Traumatic Osteo-arthritis.

This type deserves a few separate words. It is a purely localized form, in which the central part of the articular cartilage undergoes the changes that we have already enumerated owing to its being exposed to an undue degree of mechanical trauma or stress acting over a long period. Sir Arbuthnot Lane has rendered a great service by pointing out that this type is not a disease, but rather the series of compensatory changes that occurs in a joint in response to altered stress. This type, as Lane pointed out, is often occupational.

The nature of the pathological changes in osteo-arthritis supports the view that these changes are the response of the joint structures to irritation, either mechanical or toxic, and are inflammatory in nature; that these changes are both degenerative and proliferative, both processes often advancing *pari passu*; that the different reaction to the cause may largely be accounted for by the fact that the lateral articular area is better nourished than the central.

The theory of general diminished nutrition of the joint structures is negated by the proliferation—often marked—that occurs, and by analysis of the synovial fluid; moreover, arterio-sclerosis is probably not of etiological importance. Proliferative changes also negative the theory that the process is one of atrophy due to old age. Hence such a term as "*morbis coxae senilis*" is a misnomer. I venture to give the following definition: Osteo-arthritis does not constitute a disease *sui generis*, but rather the series of physiological or pathological changes that ensue in a joint when it is subjected to prolonged or oft-repeated injury, either mechanical or toxic, but of a moderate degree of intensity. The causes are therefore very varied, and there can be little doubt that the future will bring to light additional factors in its causation of which we are at present ignorant. Osteo-arthritic changes, for example, occur with greater frequency in certain disorders of the ductless glands, such as acromegaly, than can be ascribed to mere coincidence. Whether in these cases the joint changes are due to the action of toxins formed from failure of the ductless gland to supply the necessary link in the chain of metabolic endogenous products, or whether in some way the resistance of the joint to bacterial toxins is lowered, it is impossible at present to state.

The relation of osteo-arthritis to the group of auto-intoxications due to defects in the excretory apparatus or to the accumulation in the body of products of normal metabolism is still undecided, but two groups emerge concerning the etiology of which we have a little more evidence. The following preliminary classification is therefore adopted: Group 1, traumatic osteo-arthritis; Group 2, osteo-arthritis due to bacterial toxins. Examples of Group 2 are well seen after many infective forms of arthritis. It is not generally recognized that the condition may occur in certain chronic types of tuberculous disease (Fig. 4). I have also succeeded in producing an infective type of osteo-arthritis experimentally² (Fig. 5).

TYPE 2.—*Chronic Arthritis in which the Disease Commences in the Synovial Membrane (Rheumatoid Arthritis).*

Clinically every stage of acuteness may be seen, from the subacute polyarticular or monoarticular, in which pain or spasm are so marked that deforming contractures are liable to develop, to the more common type, also polyarticular or monoarticular, in which spasm or pain are less marked features, and therefore limitation of movement is less likely to accrue. Different types are also seen, which have been so carefully described by Nichols and Richardson in America and by Strangeways in this country that I do not propose to discuss them in detail.

Some little confusion has, however, been produced by the introduction of the term "atrophic." For it is now almost generally recognized, save by those who "have eyes and see not," that the process is primarily of a pronounced inflammatory nature, and that when atrophy occurs this may be largely accounted for by disuse. As in osteo-arthritis, however, degenerative changes may accompany the proliferative. These may be seen, for example, in the

articular cartilage, and the latter is often for this reason invaded and replaced by a pannus of granulation tissue derived from the synovial membrane and by ingrowths of vascular connective tissue from the subjacent cancellous spaces (Fig. 6). In the more chronic forms there may be no pannus, but mere fibrillation of the cartilage. This absence may be due to the movements of the patient which are possible owing to the less severe nature of the pain, and which militate against the progress of this tide of granulation tissue. In the synovial membrane inflammatory collections of small round cells in the vicinity of the vessels are prominent features (Fig. 7). As in the first type of arthritis, adipose tissue, cartilage, or bone may be developed in the synovial fringes. Periarticular lipping certainly occurs, although somewhat later than in the first type of arthritis. I believe it to be Nature's way of endeavouring to extend the articular surface, and is therefore more commonly seen in the more chronic cases where movement has been continued and sclerosis and contracture have not occurred.

C. SOME PHYSIOLOGICAL FACTORS UNDERLYING THE PATHOLOGICAL PHENOMENA.

I believe that the extraordinary difference between the behaviour of the central and lateral articular areas in these chronic forms of arthritis can be explained by a principle that I have endeavoured to establish—namely, that the lateral part of the articular cartilage is better nourished than the central, and is, moreover, furnished with a perichondrium in which lie blood vessels derived from the *circulus articulari vasculosus*. The central poorly nourished area responds to the cause of osteo-arthritis by degeneration, whereas the lateral part proliferates. It is possible that pressure may play a rôle—although I believe a minor one—in causing the different reaction. I found, on examination of a considerable number of cases of osteo-arthritis of the knee-joint, that in nearly every case the changes commence in the central articular areas of the patella and trochlear surface of the femur, and *not* where pressure is greatest upon the femoral and tibial condyles. The phenomena of repair of articular cartilage confirm the view of its nutrition. I was able to produce experimentally a traumatic form of osteo-arthritis by the simple expedient of removing the central part of the articular cartilage, when compensatory proliferation of the better nourished lateral area occurred, producing characteristic "lipping."³

It is instructive to study the appearances seen in cases in which a simple transverse fracture of the patella has occurred some years previously and in which the fragments have maintained good apposition. It will usually be seen that firm bony union is present; that there is usually no repair of the breach in the central part of the articular cartilage, but that the breach in the lateral portions on either side has been repaired. The adjacent articular cartilage is almost invariably fibrillated. It is probable that the condition we designate "traumatic osteo-arthritis" is in reality a physiological rather than a pathological process.

D. SUGGESTED SCIENTIFIC NOMENCLATURE.

We have already criticized some of the existing nomenclatures and offered the opinion that any attempt to classify the forms of chronic arthritis according to the supposed *nature* of the pathological changes is, owing to the complexity of the latter, undesirable.

Clinical or pseudo-clinical classification leads to great confusion. A satisfactory classification must fulfil the following requirements: it must be simple, scientific, and accurate, and non-reminiscent of mediaeval empiricism. Let us hope that an era will soon dawn when "rheumatism," "rheumatoid," and allied terms will be banished from scientific language. I suggest that the term "chronic arthritis" is simple, scientific, and accurate, since it indicates its inflammatory nature. How, then, are we to differentiate the various types? I suggest that the differentiation should be according to the site of origin, which is also the anatomical site of the principal changes. I may, perhaps, attempt to tabulate as follows:

Suggested New Nomenclature.

Chronic Arthritis (A, Monarticular; B, Polyarticular).

(1) *Synovial Type* (O.T., Rheumatoid arthritis).—The disease commences and remains more marked in the synovial membrane. The cartilage and bone may be invaded secondarily. Every gradation may be seen between the chronic types and the more acute forms which lead to ankylosis.

(2) *Chondro-osseous Type* (O.T., Osteo-arthritis).—The disease commences and remains more marked in the articular end, the synovial membrane being involved later.

(3) *Mixed Type*.—The disease commences simultaneously in synovial membrane and articular end and the changes advance *pari passu*.

In all three types osteophytes may form at the articular margins, but in the synovial type they occur comparatively late in the disease, and in the more acute forms which lead to ankylosis are usually absent. The suggested nomenclature is obviously a primary classification. It is probable that further research will justify us in subdividing each type.

E. THE NEED OF RESEARCH INTO ETIOLOGICAL ASPECTS.

Clinical evidence often appears to point to an infective or toxic origin in many cases of chronic arthritis. In a certain proportion obvious infective foci are present, the treatment of which may produce amelioration or cure of the joint condition. In other cases a careful search fails to reveal any primary focus, but it should not be forgotten that this fact by no means negatives the possible infective nature of the disease. For instance, chronic polyarticular arthritis may be ushered in by an attack of tonsillitis. The latter may entirely subside; yet the arthritis remains, and the supposition is that micro-organisms have entered the circulation via the tonsil and have settled in the synovial membrane, where they proliferate and form their toxins.

A young man came under my care suffering from chronic gonorrhoea with gleet. Gonococci were present in the prostatic smear. While under treatment he developed a spindle-shaped swelling of the interphalangeal joints of the hand exactly similar to rheumatoid arthritis. At this stage, however, examination of prostatic smears for organisms was persistently negative. The infective nature of his arthritis was therefore obvious on clinical grounds, although it could not be demonstrated bacteriologically.

Similarly in tuberculous disease of a joint the primary focus is usually a matter of assumption rather than actual demonstration. It is clear that any possible primary focus should be treated not only for these special reasons but because thereby the general health of the patient is improved.

At the same time we must bear in mind that the treatment of the primary focus need not necessarily bring about the desired result if the organisms were already entrenched in the synovial membrane and joint structures, as on clinical and bacteriological grounds sometimes appears to be the case. In these cases the treatment applied to the joints themselves is of even greater importance than concentrating on primary foci. How often the efforts of the medical man are devoted to the latter while the joints are allowed daily to become more stiff and deformed—an excellent example of a policy of "straining at a gnat and swallowing a camel."

The bacteriological aspects of the problem are clamouring for complete and scientific investigation. The important pioneer work of Blaxland and Poynton and Paine requires following up. From time to time bacteriological investigations of the synovial fluid have been made and have been usually negative. However, as an argument against the infective nature of these forms of chronic arthritis this fact is quite valueless; for we know that in the form of chronic arthritis occurring in such infective conditions as gonorrhoea the fluid is usually sterile. What is required is examination of the synovial membrane and other joint tissues. The extent of the operative field in chronic arthritis has increased of late years, and if every surgeon would make a point of having all tissues removed from the joint systematically examined by a bacteriologist the evidence obtained might be of great value. This is one line upon which my own investigations are now proceeding.

In conclusion, let me repeat that the stage is now set for

the bacteriologist and chemical pathologist in conjunction with the surgeon to march forwards, inspired by the immortal advice of John Hunter to Jenner, who was "thinking" of investigating vaccination: "Do not think but try: be patient, be accurate."

It is my pleasant duty to thank all those who have assisted me in my researches. To Sir Arthur Keith I am indebted for permission to work at the Royal College of Surgeons of England and for much help. Professor Shattock has been ever ready with advice on pathological points. To my colleagues at the hospitals with which I am connected, and especially in the Medical and Surgical Units of University College Hospital, I owe a debt of thanks.

REFERENCES.

¹Hunterian Lecture, *British Journal of Surgery*, July, 1922. ²*Ibid.*, Fig. 5. ³*Ibid.*

A CASE OF FEVER DUE TO *B. PARATYPHOSUS C*.

BY

ERIC WORDLEY, M.C., M.B., B.Ch.CANTAB.,

M.R.C.P.LOND.,

PATHOLOGIST TO THE SOUTH DEVON AND EAST CORNWALL HOSPITAL, PLYMOUTH.

PARATYPHOID C fever appears to be rare in England, and only two previous cases have been described—one by Dudgeon and Urquhart (1920) and another by Andrewes and Neave (1921). Possibly the disease is commoner than is imagined, but in many cases (as pointed out by Dudgeon and Urquhart) agglutinins are not formed in the blood, and often the diagnosis can be made only by isolation of the organism from the blood stream, or more rarely from the faeces.

A girl, aged 13½ years, was under the care of Dr. Benson Young of Plymouth, to whom I am indebted for the clinical particulars. She had had the symptoms of a mild "influenzal" attack for three to four days—temperature 100° F., pulse 120, cough, sweating, and joint pains. The temperature steadily rose, until seven days after the onset of the disease it was 106° F., pulse 124. The patient was semi-delirious, the tongue furred and dry; there were scattered areas of consolidation over the lungs, and slight diarrhoea was present. The spleen was not enlarged and no spots were noted.

At this stage I saw the patient in consultation with Dr. Young. A blood count gave the following figures: Leucocytes 4,440 per c.mm., polymorphs 54 per cent., lymphocytes 44 per cent., large hyalines 2 per cent. Agglutination to *B. typhosus* and *B. paratyphosus* A, B, and C was negative in a dilution of 1 in 25. The urine contained no pus and was sterile on cultivation. No pathogenic organisms were isolated from the faeces. From the blood a Gram-negative bacillus was isolated which gave the reactions of *B. paratyphosus* B with the exception that dulcitate was not fermented. On subculture, however, acid and gas were produced from dulcitate, though this took about seven days. Acid and gas were also produced in dextrose, maltose, mannite, and xylose; no change was produced in inositol (unlike *B. paratyphosus* B); an alkaline reaction was produced in litmus milk.

The organism was tested with some *paratyphosus* C serum kindly sent me by Professor L. S. Dudgeon. It was agglutinated to the end point of this serum, whereas with *paratyphosus* B serum, with an end point of 1 in 8,000, agglutination only took place up to a dilution of 1 in 400. On saturation of this stock *paratyphosus* C serum with the bacillus isolated from the patient the following result was obtained.

The titre of stock *paratyphosus* C serum before saturation with the patient's bacillus on its homologous antigen was 1 in 8,000. The titre of the above serum after saturation with the bacillus isolated from this patient on the same antigen was 1 in 100 = trace; 1 in 200 = 0. Although the patient's serum did not agglutinate the stock *paratyphosus* C antigen, her own bacillus was agglutinated slightly (1 in 100, trace) by her own serum.

Course of Illness.

The temperature slowly subsided and was normal in ten days from the onset of the disease. No complications ensued. The pulse throughout was high; it was over 120 during the first week of illness, and a fortnight elapsed before it was below 100.

Frequent examinations were made of the faeces, using both the brilliant green enrichment method, direct plating, and the method of drying (Wordley, 1921); in no instance was *B. paratyphosus* C isolated. Fourteen days after the first agglutination was performed the patient was again bled and her serum tested on *paratyphosus* C antigen, with a negative result.

The source of infection was not discovered and no other cases of unexplained fever arose. The faeces of the other members of the family were examined, but no pathogenic

FIG. 1.—Microscopic section of an epi-articular echondrosis (1/6 in. obj.). The deeper layer of the cartilage is being invaded by inroads of vascular connective tissue from the subjacent bone. In these inroads are many multinucleated "chondroclasts."

FIG. 3.—Fibrotic synovial fringes in later stages of osteo-arthritides. No marked alteration in vascularity.

FIG. 5.—Experiment II: Experimental production of osteo-arthritides. One c.c.m. of broth culture of streptococcus obtained from gums of case of osteo-arthritides injected into knee-joint of rabbit. Appearance after six weeks: a, commencing osteophytic growths; b, villosity of synovial membrane.

FIG. 6.—Drawing showing the typical appearances in chronic non-tuberculous arthritides of the synovial type (so-called rheumatoid arthritides). A A. Remains of the degenerate articular cartilage, in which many of the cell groups have undergone necrosis and the matrix is fibrillated in places. B B. Pannus of connective tissue derived from the synovial membrane which is spreading over the surface of the cartilage (A A), which it is invading and replacing. C C. Irruption of newly formed osseous tissue which has invaded the articular cartilage from below and joined forces with the afore-mentioned surface pannus. D D. Well marked areas of inflammatory small-cell infiltration, one of which occupies a cancellous space. See microscopic appearances of synovial membrane from this case (Fig. 7). From the knee-joint of a man, aged 45, upon whom synovectomy was performed through the author's patella-displacing approach.

FIG. 4.—Tuberculous "osteo-arthritides." Parts removed by excision from a very chronic form of tuberculosis of the knee-joint in a young adult. The synovial membrane is markedly villous, and in places contains caseous nodules. Microscopic examination shows that these contain typical tuberculous giant-cell systems. The articular cartilage is fibrillated at certain spots, and there is slight peri-articular lipping.

FIG. 2.—Synovial fringes from osteo-arthritic joint. Note vascularity with fatty infiltration in certain places. There is a complete absence of arterio-sclerosis.

FIG. 7.—Shows typical microscopic appearance of the synovial membrane in rheumatoid arthritides (chronic arthritides of synovial type). Rounded collections of inflammatory small-celled infiltration are a prominent feature.