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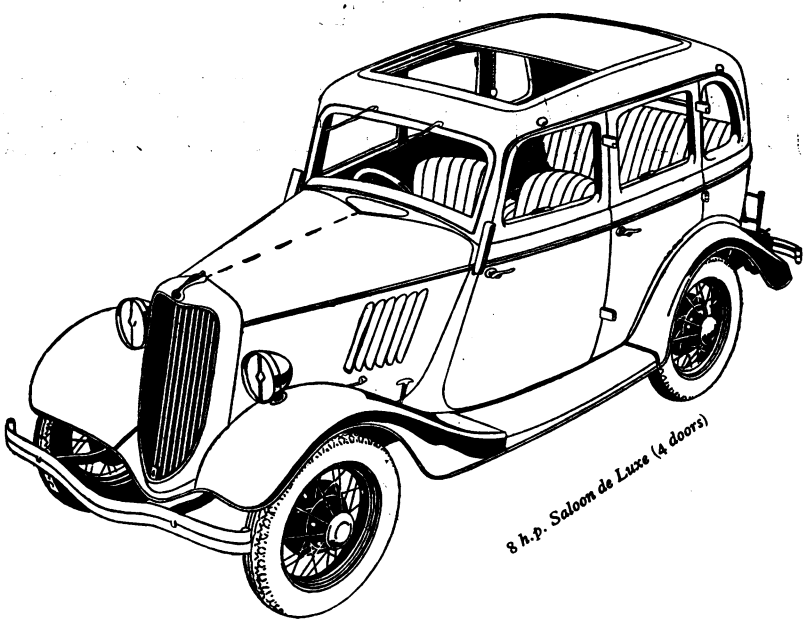

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ULSTER MEDICAL JOURNAL

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VOL. III 1st OCTOBER, 1934 No. 4

Rheumatism: and Northern Ireland

By ROBERT MARSHALL, M.D., F.R.C.P.I., D.P.H.,
from the Royal Victoria Hospital, Belfast

IT is fitting that the Editorial Committee of this Journal should have decided to devote this number to Rheumatism. First, because there is no problem of greater urgency and, with the possible exception of cancer, of greater complexity before the medical profession and the public; secondly, because Northern Ireland constitutes a particularly suitable place for the study of the many issues involved; a third, and probably the most important, reason is that the Society has the privilege of publishing Sir Thomas Houston's paper, in which he presents a new theory of rheumatism.

The social importance of the rheumatic problem can scarcely be overstated: Sir George Newman attributes to rheumatic heart disease eighty per cent. of cardiac deaths at all ages. In 1932 in Northern Ireland 3,012 persons were registered as having died of heart disease; of these 1,528 had lived in urban and 1,484 in rural districts. If Sir George Newman's estimate is correct, more than 2,400 died of rheumatic heart disease in a single year in this small community. That there are ample recruits to fall in the same battle is demonstrated by the figures of H. A. Warnock and Kenneth Cowan, which show that there are 1,100 children of school age in Belfast alone with established rheumatic heart disease, and almost 4,000 with evidence of rheumatic infection. In the year and a half ending June, 1934, 476 children were admitted to the medical ward of the Ulster Hospital: of these, 161 or 33.8 per cent. were suffering from rheumatism or chorea, with or without established heart disease.

In Sir Thomas Houston's paper there will be found a full account of the bacteriological search for the cause of rheumatism, and a new theory of its cause. If this theory can be proved, it marks an advance of tremendous importance and would settle many controversial issues, and there are few diseases so beset with controversy. We do not know what germ causes acute rheumatism: at present the researches of Coburn, Schlesinger, Sheldon, and others have adduced fresh evidence in support of Swift, Derick, and Hitchcock's suggestion that acute rheumatism is

an allergic response to hæmolytic streptococcus infection; on the other hand, Leonard Findlay, Reginald Miller, Sir Thomas Houston, and many others cannot accept this theory. We do not know whether rheumatoid arthritis is always infective in origin : many fine points of distinction between infective and "true rheumatoid" types have been made, but in practice it is frequently impossible to place a case in either category. Still's disease is a reminder that rheumatoid arthritis does occur in childhood, and conversely there is the syndrome in "persons of riper years" of acute migratory joint pains, fever, and sweating, without the carditis of juvenile rheumatism on the one hand, and without response to salicylates, but without the fusiform periarthritis and gross tendency to relapse of "rheumatoid" arthritis. Do such cases invariably escape cardiac involvement, and are they intermediate sticks of a fan whose extremes are juvenile rheumatism and rheumatoid arthritis? Most physicians regard these extremes as separate entities; support for the "essential unity" theory is found in the fact that of one hundred recent cases diagnosed rheumatoid arthritis in the Royal Victoria Hospital, eighteen had a history of juvenile rheumatism, chorea, or carditis.

Chorea presents a series of problems. We do not know why so many choreic children have repeated attacks without carditis, or whether such cases are due to a "neurotropic" type of infection. Leonard Findlay has even stated that if a child has had three attacks of chorea without developing carditis, he may have any number of subsequent attacks of chorea without danger of carditis. This does not imply that it is only the non-carditic type of chorea which tends to recur. E. C. Warner has suggested that chorea (and even articular rheumatism) may not be infective, and has stated that in chorea, uncomplicated by carditis, the sedimentation of red cells is undisturbed, which he regards as a delicate test of infectivity. On the other hand, Sir Thomas Houston and Hilton Stewart have found positive agglutination to the enterococcus in almost every choreic child examined.

That geographical distribution has some bearing on disease is undoubted, and rheumatism shows examples of this : most British physicians agree with Reginald Miller that damp houses in low-lying sites are a most important predisposing cause. In Holland such conditions are found, but rheumatic carditis is rare. In London rheumatic nodules are common, while in Belfast and in Glasgow they are apparently rare. Professor Young has recently stated that the Aschoff nodule—the essential lesion in juvenile rheumatism—is not seen in its typical form in his Belfast laboratory.

We do not know why the valves of some rheumatic hearts become the site of septic endocarditis, while others escape.

There are problems for the biochemist as well as for the bacteriologist and the physician. We do not know why forty per cent. of "rheumatoid" patients have achlorhydria, as compared with five per cent. of achlorhydrics amongst the general population. H. A. Ellis claims that "variations in the acid-base equilibrium of the body are the controlling factor in determining the character of the rheumatic invasion," but at the British Pædiatric Association in April there appeared to be doubt as to whether the rheumatic child inclined to acidosis or alkalosis. A similar

doubt appears to exist in regard to the rôle of calcium in chorea : is the blood-calcium lowered in the acute stage of chorea and does it rise with recovery? Alternatively, in cases where the blood calcium is apparently normal, Brown of Aberdeen has found good results from the intramuscular injection of calcium, and suggests that there are alterations on its diffusibility.

Uncertainty permeates our treatment even of acute rheumatism. Sodium salicylate is used all over the world, by some with enthusiasm and by others with adherence to custom. In rheumatoid arthritis a review of hospital case-sheets shows the absence of any specific treatment and a marked multiplicity of methods : the odd thing is the unanimity of optimism with which physicians and house-physicians have written the comforting word "improved" on the appropriate dotted line.

These, then, are but a few of the gaps in our knowledge of a disease which cruelly cripples and kills. I suggest that here in Northern Ireland we are well situated for its closer study and ultimate defeat. In the first place, we have not made sufficient use of our independence as a sociological unit : here in the Six Counties we have about a million and a quarter inhabitants, some living in cities, some in small towns and villages, and the remainder under rural conditions. Thus the numbers are not too unwieldy, the conditions of life are sufficiently varied for co-ordinated inquiry into age-incidence and topographical distribution, as well as clinical, bacteriological, and biochemical phenomena. The mechanism required for such an inquiry already exists in an almost complete state. The Senior Medical Officer of the Ministry of Home Affairs has already shown his practical interest in the problem, and is in a position to correlate the work of the various State medical services. The Registrar-General is also statistician, and is keenly interested and helpful. School medical services have been organized in Belfast, Londonderry, and throughout the Six Counties : their medical officers are already collecting valuable data. The physicians of the Belfast Medical School have published various papers on the subject. Doctors in general practice represent the first line of attack on disease. The new Pathological Institute has accommodation and, better still, the skill and enthusiasm of Professor Young and his colleagues. Finally, the recent liberation of Sir Thomas Houston from the insistent demands of routine hospital duties gives him an opportunity to follow his researches on the rôle of the enterococcus to definite and, we hope, a successful conclusion.

It should not be impossible to forge a link which will unite these varied activities. At present it must be admitted that our several efforts are sadly lacking in cohesion : collaboration is, in my opinion, most likely to be achieved by the formation of a Rheumatism Research Committee for Northern Ireland, to be representative of all the activities I have already named.

Money would be required for the prosecution of the laboratory work involved, and for adequate clerical assistance, but there is no object for which public money could be spent with better hope of public good. The sum involved—for example, a grant of £1,000 a year for three years—is trifling compared with the present cost in money of the ravages of the disease apart from its toll in suffering, death, and bereavement. *Pro tantulo quid recipiamus?*

A Theory That May Account for the Bacteriology of Rheumatism

By Sir Thomas Houston, o.b.e., b.a., m.d.

from the Clinical Laboratories, Royal Victoria Hospital, Belfast

In June of last year the Arthritis Committee of the B.M.A. published their report.[1] Chronic rheumatism has been described by them under the following headings :—

(*a*) Primary rheumatoid arthritis.
(*b*) Secondary rheumatoid arthritis.
(*c*) Chronic villous arthritis.
(*d*) Osteo-arthritis.
(*e*) Spondylitis.
(*f*) Fibrositis.

The Committee admit at the outset that an etiological classification is, in the present state of our knowledge, impossible, and that a clinical grouping has been adopted which is unsatisfactory in some respects. The report, however, is an able one, and well deserves the perusal of every student of this important subject.

The implication of this report is that all these conditions are essentially and etiologically different, and in a general way most physicians will agree that these conditions are in their clinical features often distinct, but if one considers the individual patient and his or her rheumatic manifestations at different periods, he will often find it more difficult to relegate their disease to one definite category. He will find patients who have a definite history of fibrositis and have now osteo-arthritis or rheumatoid arthritis, or in one patient he may find one joint that corresponds to an osteo-arthritis and another in the same patient to a true rheumatoid arthritis, or a case with cardiac rheumatism may develop a typical rheumatoid arthritis.

Fifty years ago rheumatoid arthritis was held to be a manifestation of gout, and called rheumatic gout. Some ten years later it was closely linked to tuberculosis; while in the following decade it was said to be a neurosis in the sense of a neural arthropathy. In more recent years a rheumatic diathesis has been postulated, and again, at least with reference to that variety we are now to call chronic villous arthritis, the disease was supposed to be mainly due to endocrine dysfunction.

Sir Jonathan Hutchinson said rather whimsically that wherever arthritis occurs in connection with food we call it gout, and wherever such association is wholly absent we call it rheumatism. The controversy then took on a rather revolutionary claim, namely, that whatever else chronic joint disease might be, it certainly was not rheumatism. It was to enforce this doctrine that Sir Archibald Garrod proposed the term rheumatoid arthritis, which has persisted to the present day.

It is perhaps savouring of political polemics to remind Sir Humphry Rolleston, the chairman of the Arthritis Committee, of his address at the Bath Conference on Rheumatism in 1928.

He said : "Whereas at one end of the scale there is acute rheumatic fever, which may mainly or exclusively attack the heart, there is at the other end osteo-arthritis, which is mainly, if not entirely, a degenerative lesion that does not induce cardiac lesions and does not respond to salicylate treatment. Between these two extremes is a chain of gradual transitions. Clinically it may be hard to decide if, when after acute rheumatism what is commonly called rheumatoid arthritis develops, a different pathological process has been implanted, or whether or not the same process, though modified in its characters, is responsible for the whole sequence. Is the occurrence of chronic joint disease in persons formerly attacked by rheumatic fever sufficiently common, as Coates argues, to suggest that the two diseases, as they are usually regarded, are due to the same infection, or is the sequence more credibly explained by the supposition of a general arthritic diathesis?"[2]

Sir Humphry then makes appeal to the structural lesions that occur in rheumatic disease, and shows that 'Aschoff's bodies' seem to occur not only in cardiac disease, but also in rheumatoid arthritis, Still's disease, and osteo-arthritis. Hawthorne in 1912 said: "Either rheumatoid arthritis is rheumatism, or the development of fibrous nodules in the subcutaneous tissues is not a special note of rheumatism."[2]

The question of the distinction between primary and secondary rheumatoid arthritis does not seem to me to be quite clear to the Committee, if such a distinction can be maintained. Douthwaite says that focal sepsis can and does produce multiple arthritis without the aid of other factors, dietetic or otherwise. Such a condition should be termed infective arthritis, and is totally distinct from the rheumatoid variety. Douthwaite gives us the distinguishing points of infective arthritis :—

(1) Excess of synovial fluid;
(2) Intense synovial congestion;
(3) Osteo-arthritic changes begin early;
(4) Muscular wasting not marked;
(5) Adhesions are the rule;
(6) Dilatation of the blood-vessels of the skin.[3]

I quite agree with Douthwaite that there are many typical cases of rheumatoid arthritis that have no obvious septic foci, but apart from the presence or absence of a septic focus it may be impossible to distinguish the two conditions.

Thomson and Gordon, both members of the Arthritis Committee, say in their book on chronic rheumatic disease: "One of the most serious forms of chronic rheumatic disease is that form of multiple arthritis which results from chronic focal sepsis and which has been described under the name of rheumatoid or atrophic arthritis. The part played by focal sepsis in the causation of this disease is so important that we propose to drop the older nomenclature and to substitute the term 'focal arthritis' instead. The name 'rheumatoid arthritis' conveys no suggestion of the main etiological factor, and may even mislead by suggesting a false relationship to rheumatic fever. On the other hand, the term 'focal arthritis' not only emphasizes the underlying cause, but serves as an emphatic reminder to the medical attendant that it is his duty to find out where the infection lies, and to treat it thoroughly and efficiently at the earliest possible moment."[4]

Again, Dr. Russell L. Cecil of New York has on blood-culture grounds come definitely to the opinion that all cases of rheumatoid arthritis are of streptococcic origin. By a special method of blood-culture he has, in sixty-eight per cent. of the cases examined, isolated an atypical streptococcus from the blood and also from the joints.

The most striking characteristic of these streptococci is the very slow growth of the first generation in broth. The average time of the appearance of this streptococcus was 15.7 days, but ranges from four to thirty days.

Some twenty years ago, when I began to take an interest in rheumatism, I was convinced that cardiac rheumatism and chronic arthritis were totally different conditions and had probably a totally different etiology. I have, however, latterly come to doubt whether this view was altogether correct. Reading the views of others has had its influence, as quite a number of the distinguished students of rheumatic disease have held the view that the different forms of rheumatism were etiologically connected. Poynton and Payne, Carey Coombs and Coates, who all made a lifelong study of rheumatic conditions, held this view.

There is an acute disease which I have usually called 'subacute rheumatism,' which has often impressed me. This disease may have an acute or an insidious origin, and is accompanied by a fairly high fever, profuse sweating, and migratory polyarthritis, and it may not be much influenced by salicylates, but is by such drugs as aspirin and novalgin. It occurs in an adult or middle-aged patient. It has no cardiac manifestations, and this is the sole clinical distinction from a typical case of rheumatic fever. The patient usually gets quite better, but may have a residual arthritis which may trouble him for years. Several cases of this kind have occurred amongst my friends, so I know exactly what has happened to them.

The question that arises is—Is this rheumatic fever in the adult, minus the cardiac manifestations? It is now pretty well recognized that true rheumatic fever is a disease of childhood or adolescence.

Latterly I have come across a good many cases of chronic rheumatism with a cardiac history. Are we to conclude that such patients have a double infection, or admit that both conditions may have a similar etiology?

I should also like to add that there are three great basal infections in medicine, viz. :—(1) Syphilis, (2) tubercle, and (3) rheumatism. These diseases have many analogies in their acute and chronic manifestations. A physician, when he has examined a case, will often say to himself, This might be syphilis or tubercle, or it might be rheumatism—and it is often difficult to decide which it is. All these diseases have protean manifestations. Who would decide on clinical grounds alone, that primary syphilis, secondary syphilis, the gummatous and rupial manifestations of tertiary syphilis, the locomotor ataxias and G.P.I.'s, or the Charcot's joints, had one common etiology; or what physician unaided by Koch's work and the bacteriological and histological findings could have arrived at the conclusion that phthisis, tuberculous meningitis, tuberculous peritonitis, tuberculous adenitis, tuberculous enteritis, not to mention lupus and the skin lesions of tubercle, were all manifestations of one infection?

It would seem to me that the etiological factor, when this is finally determined, may illuminate the difficulties and reconcile the discrepancies of the rheumatic problem. I think we should still keep our eyes open to the possibility that rheumatism in many or all of its manifestations might be due to one basal infection, just as is the case with syphilis and tubercle.

It would be quite impossible, in the time at my disposal, to review the immense literature that has accumulated with regard to the bacteriology of rheumatic conditions. At the beginning of this century the work of Leyden, Popoff, Triboulet, Coyon, Wassermann, Poynton and Payne, Singer, Beattie, Beaton and Ainley Walker seemed to promise a solution to the question, and the *diplococcus rheumaticus* was held to be the etiological factor in rheumatic fever and rheumatism generally. As the streptococci isolated by these numerous observers were not defined by present-day standards, it is now impossible to state how many of these organisms isolated by these various workers were the same. It is interesting, however, to note that Thiroloix, who first described along with Achalme the bacillus known as Achalme's bacillus, believed it to be the anærobic form of the enterococcus. He did a series of experiments which he believed showed that this bacillus was not the bacillus of Welsh and could undergo transformation into the enterococcus. For many years this theory about Achalme's bacillus had died a natural death, but, strange to say, has recently been revived by Bertrand of Antwerp, who read a remarkable paper on this subject at the Bath Conference on Rheumatism in 1928.[5]

It is doubtful now whether the various cocci said to be the *diplococcus rheumaticus* were the same organism, but a number of these cocci were enterococci, and Beattie's strains have been kept, and still give the fundamental characteristics of this group of organisms.

In 1906 William Bulloch, in an able review of the whole question, came to the following conclusion: "In spite of the numerous investigations that have been carried on, it seems to me that the etiology of rheumatic fever belongs to the arcana of pathology, and although what the clinicians call rheumatic fever is probably a specific infective disease, 'the virus is not known.' "

From this time on the Americans evidently decided that they would take practical steps to settle this question once and for all.

As a result, several very remarkable contributions have come to us from across the Atlantic.

Clawson in 1925[6] has described his observations, in which strains of streptococcus viridans were isolated from twenty cases of well-defined acute rheumatic fever, rheumatic endocarditis, or chorea, of which thirteen were derived from blood-cultures during life. The high percentage of positive blood-cultures is attributed by him to his technique. He took 20 c.c. of blood and put this in two test-tubes and allowed it to clot. The clots were loosened and put into flasks of 250 c.c. glucose broth. This streptococcus belongs to the viridans group, and in many cases ferments mannite—morphologically it resembles a pneumococcus. It does not appear to be a specific strain, as an agglutinating serum only reacted with some of the strains.

In 1927 Small gave a convincing account of his work. He says :[7] "A serologically specific non-hæmolytic streptococcus with distinctive histological characters has been isolated from the blood- and throat-cultures of patients with rheumatic fever, and from cultures of the fæces in a few patients with chronic arthritis."

It is interesting to note that his positive blood-cultures appeared, one on the ninth and the other on the nineteenth day of incubation.

The coccus had no effect on blood-agar, did not ferment mannite and fermented inulin; injected into rabbits, he states that it produced arthritis and cardiac disease, and in the subacute stages Aschoff's nodes in the myocardium.

He claims remarkable therapeutic effects from sera and vaccines made from this organism. He calls the organism 'streptococcus cardio-arthritidis,' and offers it as the cause of rheumatic fever.

On reading Small's paper, one would imagine that the problem had been solved.

In the same year, 1927, Birhaug[8] also published his results, and claimed to have isolated a similar coccus from rheumatic cases. It also produced no change on blood-agar, fermented inulin, and was a toxin producer. He found that a great number of rheumatic patients were allergic to the toxin derived from this streptococcus. By injecting his toxic filtrate into himself, he produced a migratory polyarthritis that had the characters of rheumatic fever and yielded to salicylates.

Birhaug, however, in a second paper, is not so sure that his coccus is the cause of rheumatic fever, but has put forward the theory that a specific soluble toxin may be produced by a group of serologically unrelated streptococci, and that the clinical syndrome of rheumatic fever may be provoked by a long fixation of the toxin in certain tissues.

The only worker in this country who claims to have confirmed the isolation of these streptococci is Lazarus Barlow, who compared eleven strains of cocci which he isolated from rheumatic cases and found that they had a close relationship.

Schlesinger, with the help of Hedley Wright, endeavoured to confirm the work of Birhaug, but, using his technique, they failed to isolate Birhaug's coccus from the throats of active cases of rheumatism.

Then came the very remarkable results of Cecil, Nicholls, and Stainsby,[9] using a method of blood-culture that has already been mentioned in connection with rheumatoid arthritis.

Twenty-nine cases were studied in 1928, and gave positive results from blood-cultures in thirty-one per cent.

Thirty-one cases were studied in 1929, and these gave eighty-three per cent. of positive results.

The organism obtained was a streptococcus growing in couples or short chains, and proved in thirty-three out of thirty-five strains to be a streptococcus viridans or alpha streptococcus—one was streptococcus hæmolyticus and one was a gamma streptococcus.

In seven cases of acute rheumatism the synovial fluid was examined, and positive results were obtained in five of these. Here again a noteworthy point was that the

positive blood-cultures appeared after an incubation of seventeen days, and in the case of the arthritic cultures about the eighth day.

These results of recent American investigations present some very remarkable features.

(1) The greatest trouble was evidently taken with the technique.

(2) It must be considered, however, that many other workers have recorded negative results from blood-cultures in these conditions.

(3) Cecil, however, is quite convinced that such negative results are failures owing to imperfect technique.

(4) It seems quite clear that similar methods of blood-culture should be tried by other workers on a larger scale.

The difficulties of the situation and the multiplicity of the streptococci found have no doubt inspired the hypersensitization view, which is probably the most fashionable theory at the present day, unless we accept the still more recent view suggested by Coburn,[10] and supported by Colles and by some workers at Great Ormond Street, that the hæmolytic streptococcus is the real cause of rheumatic fever.

The sensitization view is put forward by Homer Swift, Derrick, and Hitchcock,[11] and supported by Zinsser and Yu. They hold that a chronic allergic state is set up by the existence of septic foci such as the tonsil, and that this gives rise to the dermal reactions that have been studied so thoroughly by Coburn, Birhaug, Colles, and others, and that this sensitization may reveal itself on appropriate stimulus by the syndrome of rheumatic fever with its classical heart and joint manifestations, just as a dose of serum may produce a sensitization arthritis.

The objections to this view are, to my mind :—

(1) It is inspired by the fact that it would explain the difficulties of the bacteriology of the disease.

(2) It is quite contrary to the analogy of tubercle and syphilis, which have many points of resemblance to rheumatism. For instance, if we did not know that the tubercle bacillus was the particulate cause of the various tuberculous lesions, we could explain these manifestations on a sensitization theory, and there can be no doubt that sensitization phenomena are exceedingly well marked in tubercle, but such sensitization alone cannot explain the tubercular nodule and the pathogenesis of the disease.

(3) It does not therefore explain the Aschoff's bodies and fibrosis of the heart valves. Are any similar structural lesions found in a true sensitization arthritis?

(4) Why should this sensitization process be confined to streptococci?

(5) Why should this postulated sensitization affect only a limited number of the community when streptococcic throat invasions are so prevalent?

(6) A latent focal infection springing into activity and liberating an excess of sensitizing substance should produce a local allergic response of the type of the Arthus phenomenon. The active products should tend to be destroyed *in situ* rather than be capable of accumulating to a sufficient extent to undergo dissemination and produce general symptoms.

(7) I have always thought it more likely that the exacerbations of rheumatic conditions that do undoubtedly occur after tonsillitis and other infections, are due not to a pure sensitization process, but to the activation of the virus of the disease. The same occurs very commonly in tubercle, where a more or less latent tubercular focus may be stirred into activity by some intercurrent infection.

Although it is against all bacteriological analogy that a definite clinical entity should have a varied microbic etiology, yet this theory of sensitization is undoubtedly ingenuous, and would account for many of the difficulties, but I cannot bring myself to believe that it is the correct explanation.

The difficulties of these recent results from America are :—

(1) That different types of streptococci have been isolated by different workers.

(2) The new work of Small and Birhaug, which shifts the onus from the streptococcus of the viridans class to those that produce no change in blood media, does not help us much, provided this distinction is an essential one.

(3) In the majority of these recent papers special methods of blood-culture were adopted, and the infecting coccus took several weeks to grow out.

The last result needs careful consideration, because we know that if any sub-cultured laboratory coccus be planted in blood broth it will grow out with certainty in twenty-four hours. In other words, if these results are of any significance, there must be some restraining influence that prevents rapid growth of the coccus in the culture flask.

There is, however, a well-defined clinical condition which has many claims to be called a clinical entity. Different views are held with regard to its association with rheumatism. Some have held that it was simply a malignant form of rheumatic fever, while others believe that it is a secondary infection grafted on an old rheumatic heart, and it is held that this syndrome frequently occurs in cases of congenital lesions of the heart, and that this association favours the view that there is a superadded infection in cases of chronic ulcerative endocarditis.

The facts about blood-cultures in this condition are :—

(1) The great majority of positive cultures prove to be an alpha streptococcus (viridans).

(2) Quite a number of cases have been reported in which streptococcus fæcalis has been isolated.

(3) It is interesting to note that in very malignant cases (i.e., running their course in a few weeks) streptococcus zymogenes has been recovered.

(4) In quite a number of cases of this disease, blood-cultures may be persistently negative.

(5) In a given case, if the blood-culture is once positive, it is generally always positive.

Looking at the cocci which have been isolated from this condition, from a historical point of view there are several points that claim our attention :—

(1) In 1909 Horder has recorded the isolation of eight strains of streptococcus fæcalis from cases of ulcerative endocarditis.

Wright has recovered from the blood one strain of this coccus in forty-five cases.

(2) From cases described as malignant endocarditis the streptococcus zymogenes has been isolated—

1. By MacCallum and Hastings (1899).
2. By Braxton Hicks (1912).
3. By Warren Crowe from three cases (1923).
4. By Houston (2).

This organism is the liquefying form of the streptococcus fæcalis or enterococcus.

(3) By far the greater number of positive cultures have been classed as streptococcus viridans, but several workers have noted that such strains are peculiar.

(*a*) Rosenow,[12] Libman, and Allen advanced the view that this streptococcus is a modified pneumococcus. According to Rosenow, these modified pneumococci produce a green coloration on blood-agar, and most of the strains ferment inulin. They grow on artificial media exactly as pneumococci grow when they are subcultured many times. He believes that these streptococci belong to one and the same species, and he considers the several strains resemble pneumococci rather than streptococci.

(*b*) Ainley Walker[13] in 1912 brings forward as evidence of the unreliability of sugar fermentation tests in the differentiation of streptococci, his experience with a streptococcus freshly isolated from a case of ulcerative endocarditis. Altogether fifteen changes of reaction occurred and four new sets of reaction developed.

(*c*) Dudgeon, Bawtree, and Corbett[14] in 1916 give another example of the changing fermentation reaction in a streptococcus isolated from a case of ulcerative endocarditis.

(*d*) Hedley Wright[15] points out that although the streptococci isolated from cases of chronic ulcerative endocarditis are practically all classed as streptococcus viridans or alpha streptococci, all reports, however, agree that the streptococci isolated from these cases are quite heterogenous as to their biological reactions and also when tested serologically. The disease, however, is a very definite clinical entity and its relationship to rheumatic endocarditis much discussed.

The presence of this type of streptococcus in the blood in Wright's experience invariably meant the existence in the patient of subacute infective endocarditis. This is the common experience, though several exceptions to this rule have been recorded.

In the serum of the patient, antibodies may usually be demonstrated. The general resistance of the patient to the infecting organism seems, as far as can be judged by *in vitro* experiment, to be of a high order, yet the disease invariably goes on to a fatal issue.

(*e*) In the cases of ulcerative endocarditis in which we have obtained positive cultures we have noted two points :—

(1) The change in the flask indicating a positive culture was frequently not noticed for two or three days; occasionally it took nine days before a positive culture was obtained.

(2) In all cases the subcultures from the first blood-agar plate were difficult to grow, and grew in a clumpy granular way.

The points that I wish at present to direct your special attention to in this survey of recent bacteriological work are :—

(1) The extreme difficulty of growing streptococci from the blood of acute rheumatism and other rheumatic conditions; many observers have got quite negative results.

(2) In recent work where positive results have been obtained, two things seem clear—(*a*) special technique has been adopted, and (*b*) the coccus has often taken as long as three weeks to appear in the blood-culture flasks.

(3) The streptococci, though generally classed as 'viridans' or alpha streptococcus, have generally been biologically and antigenically different.

I wish you to contrast these observations with what is known to occur in cases of chronic ulcerative endocarditis.

(1) Although all observers record positive cultures in this disease, in a good many cases of the same disease no culture is obtained. This feature has been often commented on.

(2) A positive culture when obtained is often difficult to grow on subculture, and may take several days before it appears in the blood flask.

(3) The cultures when obtained are all antigenically and biologically different, although many observers have mentioned the fact that these streptococci seem to belong to a peculiar type of viridans streptococci.

I wish now to direct your attention to a totally different line of research—one that is of paramount importance in modern bacteriology, and one that is destined to alter fundamentally many of our orthodox concepts about micro-organisms. I refer to the work that has been done on the bacteriophage ever since D'Herelle made his fundamental observation in 1917.

You all know something of this wonderful lytic principle that has the miraculous power of dissolving sensitive bacteria, and that this principle may act in dilution of 100—1,000 millions, and that this principle can be transferred from one culture to another *ad infinitum*.

D'Herelle has held against all opposition that this principle is of the nature of a living virus that obtains its food from living microbes and can grow only at their expense.

I wish specially to direct your attention to the effect of the bacteriophage upon sensitive bacteria.

Though with a highly potent or virulent bacteriophage the bacteria are all dissolved and the fluid remains sterile indefinitely, this does not always or generally happen, but after several days or longer a secondary culture arises. Such secondary cultures often show marked differences from the typical parent stem. The predominant types are :—

(1) Strains merely resistant to lysis.

(2) Lysogenic strains.

These strains have incorporated with them the lytic principle.

They are regarded as 'contaminated' strains by D'Herelle. They can initiate lysis in sensitive strains, but may not themselves show evidence of lysis. They can be sub-cultured for long periods of time and still retain their lysogenic properties.

(3) The secondary cultures often tend to grow ill in fluid media, and often form agglutinated masses at the bottom of the tube.

(4) On solid media they often form irregular, ribbed colonies, the 'flatter-formen' of Gildemeister.

(5) These cultures are usually inagglutinable by specific sera.

(6) The biological reactions may be quite altered, and Gratia has shown that the characters of an organism may be so variably altered that as many as eleven different forms may arise from a single culture from the action of the lytic agent.

(7) These variants are in many cases temporary, and when subcultured will revert to the original culture, and thus can be definitely recognized. In some cases, however, this reversion may be difficult to accomplish. D'Herelle has detailed the methods that he found most successful in causing this reversion, that is, in purifying his mixed cultures. D'Herelle's ultra-pure colony is one that is free from bacteriophage symbiosis. In many cases the variant, however, may become a permanent mutation. Indeed, D'Herelle favours the view that all fixed mutations occurring among bacterial species are produced through the action of the bacteriophage. It is quite certain, however, that the bacteriophage is a most powerful factor in producing bacterial variation.

We must now consider the Belfast work on the enterococcus.

The work that has been done on this subject for the last twenty years has convinced us that this organism is one of great interest and importance. In many conditions it is an important infective agent, and seems to be specially associated with rheumatism in many of its clinical manifestations. In a previous communication before this Society I have discussed this problem, and given my reasons for believing that the originators of this conception might be nearer the truth than is generally supposed. I will again briefly detail these reasons.

(1) In rheumatic cases this organism can be frequently isolated from such sources as :—

(*a*) The urine;
(*b*) Septic tonsils;
(*c*) The root canal of septic teeth;
(*d*) From post-nasal catarrh;
(*e*) Septic antra and sinuses;
(*f*) Gall-bladders after excision;
(*g*) Abscesses in various parts of the body;
(*h*) Certain forms of acne and other skin lesions;
(*i*) Invariably from a chronic form of onychia, occurring usually in women.

In such situations the enterococcus usually occurs in mixed culture—bacillus coli, staphylococci, streptococcus viridans, and other organisms are frequently found in association with it. The relations of such septic foci to rheumatism have, ever since William Hunter's time, been regarded as of great clinical importance.

(2) A great number of agglutination tests in many rheumatic conditions have convinced us that this coccus is infecting the patient.

(3) In some acute cases the enterococcus has been isolated from the joints and from the blood.

(4) Rheumatic patients are usually extremely sensitive to small doses of an enterococcic vaccine.

(5) We have previously discussed the relation of chronic onychia to rheumatic conditions, and have found this lesion associated with some cases of arthritis, with colitis, and even with acute cardiac rheumatism. The popular idea that this lesion is an indication of rheumatism is, we think, well founded.

(6) The detailed study of numerous individual cases has convinced us of the importance of infection with the enterococcus.

The study of this organism, however, has been largely neglected, as many bacteriologists seem to regard the enterococcus as a harmless saprophyte of the bowel, of no pathological importance, and therefore are inclined to relegate it to oblivion. In English literature there are only a few good papers dealing with this micro-organism, one by Dible (1921), and one by Bagger (1926), and lastly, the article by Dible in the Medical Research Council's System of Bacteriology. I am glad to find that these articles go very fully into the characteristic heat-resistance of the organism, and amply confirm the observations made by Captain McCloy and myself in France. These observations were published in two papers, one in 1916 and another in 1920. The importance of this test is now such that an organism having the morphology of the enterococcus, and which also conforms to this heat-resistance test, may with certainty be classed as an enterococcus. The possibility of a true enterococcus losing its power of thermo-resistance is an interesting problem, but with our present knowledge and methods may be a difficult matter to establish, though there is reason to believe the solution of this problem may prove of great theoretical and practical importance.

We wish now to propose another interesting test for the enterococcus, which in Belfast we have found of great value. We trust it will obtain the same conclusive confirmation that the heat-resistance test has received.

The fact that enterococci grow in bile, while other streptococci do not, has been mentioned in recent literature by several observers, but the fact that enterococci invariably grow in long chains in pure bile does not appear to have been observed. In Belfast we frequently use this test to distinguish enterococci from other varieties of streptococci and also from staphylococci. It is our experience that this organism invariably grows in pure bile in long chains of twenty or thirty cocci, and that no other organism has this property. By means of these two tests it can practically invariably be decided whether a coccus should be classified as an enterococcus or not.

The next point which I wish to mention is the pleomorphism of the organism. This property was noted by the original French writers on this subject. It is interesting to note that Thiroloix regarded Achalme's bacillus as an anærobic form of the enterococcus. There is undoubtedly a tendency in many media for the entero-coccus to assume a bacillary form. If, for instance, we examine an impression

preparation of a colony of pure enterococci four or five days old, we find the centre is composed of gram-negative cocci, while the periphery often contains many bacillary forms among typical lanceolate enterococci. Such bacillary forms may even recall the appearances of Bacillus Welsh.

On media, such as agar or chocolate, the enterococcus may grow in a form that closely resembles the staphylococcus, and sometimes cannot be distinguished from this organism microscopically. It is under such circumstances that the growth of the organism in bile is a useful method of distinction. The enterococcus, as already mentioned, grows in chains, while the staphylococcus grows in clumps. The enterococcus usually grows in most media in the diplococcal form, and only very short chains are found, but when grown on blood serum, especially if the serum agglutinates the enterococcus, very long chains are found, and as already mentioned, the enterococci invariably grow in bile in this characteristic way. I think, therefore, we are right in describing the enterococcus, as the original French writers did, as a pleomorphic streptococcus.

It is frequently stated that the enterococcus is devoid of action on red blood corpuscles, causing neither methæmoglobin formation nor hæmolysin. This method of stating the appearance of the growth on blood-agar is quite a mistake, and has frequently resulted in true enterococci being regarded as belonging to the so-called 'viridans' group, or even to the hæmolytic group of streptococci. A certain number of enterococci might be so described, but many strains of enterococci do produce very definite changes on blood-agar plates, while a few produce a definite zone of hæmolysis. It is stated that when this area of hæmolysis does occur, these cocci do not give any hæmolysis when tested by McCleod's method, and that the hæmolysis produced on the blood-agar plates is due to digestion and not to a true hæmolysin. This subject, I feel, needs further work before a definite opinion can be expressed. Such qualities in the strains investigated have proved to be permanent qualities as far as the individual strain is concerned, and are apparently not related to their antigenic structure.

It has been stated that this group of organisms show no serological homogeneity, and Bagger concludes that the individual organisms are strain-specific and that the reaction is therefore useless. We hope to show that this statement is quite erroneous, and it would seem strange if nature worked in this haphazard way with a definite organism such as the enterococcus. By the use of the heat-resistance test it has been our custom to attempt to isolate this organism from various sources in the human body. Each enterococcus so isolated has been systematically studied, its sugar reaction done, and its antigenic relations investigated. Enterococci have been frequently isolated from such sources as :—

(1) The urine;
(2) Septic tonsils;
(3) The root canal of septic teeth;
(4) From post-nasal catarrh;
(5) From septic antra;
(6) Gall-bladders after excision;

(7) Abscesses in various parts of the body;
(8) Certain forms of acne and other skin lesions;
(9) Invariably from a chronic form of onychia, occurring usually in women.

From the study of many individual cases I have been forced to the view that the presence of the enterococcus in such abnormal situations is not an accidental finding, but frequently means that this organism may be an important infective agent in the septic conditions concerned.

Some years ago, seventeen strains of enterococci were isolated—the majority coming from cases of chronic onychia. These strains gave identical colonies on agar and Conradi Drigalski's medium, had all the same sugar reactions, all gave the characteristic tests for enterococci, and on microscopic examination appeared exactly similar, and all gave suitable diffuse growths in broth for agglutination purposes. A serum was prepared by inoculating a rabbit with one of these strains (Campbell).

The following was the result :—

AGGLUTINATION WITH RABBIT'S SERUM—RABBIT INOCULATED WITH THREE DOSES OF CAMPBELL'S COCCUS, 9th February, 1928.

		1/100	1/200	1/500	1/1000	Control	
(1) Bississar	(P)	—	tr	tr	—	—	R
(2) Campbell	(T)	+ +	+ +	+ +	+	—	S
(3) Campbell	(O)	+ +	+ +	+ +	+	—	S
(4) Barnes	(T)	—	—	—	—	—	R
(5) Barnes	(O)	+ +	+ +	+ +	+	—	S
(6) Craw	(O)	—	—	—	—	—	R
(7) Drain	(O)	—	—	—	—	—	R
(8) Drennan	(O)	tr	—	—	—	—	R
(9) Foster	(O)	—	—	—	—	—	R
(10) Hughes	(O)	—	—	—	—	—	R
(11) Jordan	(O)	+ +	+ +	+ +	+	—	S
(12) McMaster	(B)	+ +	+ +	+ +	+	—	S
(13) Rainey	(T)	+ +	+ +	+ +	+	—	S
(14) Rainey	(O)	—	—	—	—	—	R
(15) Sharpe	(O)	+ +	+ +	+ +	+	—	S
(16) Gordon	(O)	—	—	—	—	—	R
(17) Massey	(O)	+ +	+ +	+ +	—	—	S(?)

It will be seen that seven of these strains all agglutinated to the full titre of the serum, while the other ten did not agglutinate at all, or only in one or two of the lower dilutions. The serum at first used was a low-titre serum, the result of two intravenous injections into an ear-vein of the rabbit, so the experiment was repeated later with a stronger serum, but with the same result, except that a large number of the ten non-agglutinating strains were thrown down in the lower dilutions. I was at first at a loss to determine the reason of such striking and definite results.

At this time I was reading one of Arkwright's papers on the rough and smooth forms of bacilli, and it occurred to me that this might be the explanation, although I could detect no colony difference in the strains concerned. When, however, I examined with a hand lens the controls after the test racks had been several hours in the water-bath, I found a clear-cut difference between them. The controls of the strains that did not agglutinate were all faintly granular, while the controls of the strains that agglutinated to the full titre were perfectly homogeneous, non-granular emulsions.

All the strains used in this experiment were then tested systematically, and found to have the following differences. The agglutinating strains were all found to liquefy gelatine and did not deposit rapidly when grown in two per cent. glucose broth; they withstood boiling without becoming granular.

On the other hand, the strains that did not agglutinate properly did not liquefy gelatine, deposited rapidly in two per cent. glucose broth, and became granular on boiling. We found that the coccus (Campbell) with which the rabbit was inoculated was a perfect coccus in the sense that it made a beautiful opalescent emulsion which did not become granular on prolonged boiling and was quite as stable as the emulsion made from the typhoid bacillus, and that the other strains that liquefied gelatine had almost identical properties.

This coccus we called type A, and used for many months for agglutinating purposes. Later on, as it seemed not to be quite so good, we replaced it by another strain with identical antigenic properties isolated from a septic tooth of a case of pyrexial rheumatism, and this coccus after almost three years' use still makes a perfect emulsion for agglutinating purposes.

Working with this type A strain, we found that in quite a number of the cases from which we had isolated enterococci from abnormal situations, the serum of the patient gave a definite agglutination, while the controls did not. We also found in quite a number of similar cases, where we expected to get a similar agglutination, that we got a negative result.

This history of the isolation of type B coccus is also interesting. We had read Bargen's papers on the isolation of a diplococcus from cases of chronic ulcerative colitis, and we determined to attempt to isolate the coccus which he described from cases of this disease. From four cases of very severe ulcerative colitis we isolated four non-mannite fermenting cocci which seemed to correspond to Bargen's description of his coccus. We sent these four strains to Bargen, and he kindly examined them exhaustively and replied that these strains were similar to those with which he was working. These cocci were all heat-resisting enterococci that did not ferment mannite, and similar strains could frequently be isolated from cases of ulcerative colitis, but we also isolated cocci of the same kind from cases that were *not* ulcerative colitis. One point that puzzled us about Bargen's coccus, assuming that he was correct in regarding it as the bacterial cause of chronic ulcerative colitis, was the fact that although we did numerous tests we could not get this coccus to agglutinate at all with the sera of cases of ulcerative colitis, nor could

we get any complement deviation. We finally gave the matter up after many months of hard work.

One of the cases of severe ulcerative colitis developed an abscess in connection with an appendicostomy wound, and the pus was cultured. We were astonished to find that all the enterococci isolated from the pus were liquefying enterococci and formed depressed blackening colonies on chocolate media; further, they proved to be perfect forms of the coccus in the sense that they did not deposit in two per cent. glucose broth and also withstood boiling without becoming granular, but on being put up against type A serum this coccus did *not* agglutinate, or only in the lower dilutions. The same patient had occasion to get a tooth extracted, and from the fang of this tooth a similar liquefying type of enterococcus was isolated along with a coli. Then again, this patient developed an attack of broncho-pneumonia, and from his sputum by the heat method another similar liquefying enterococcus was isolated. A serum was then prepared by inoculating a rabbit with one of these enterococci, and it was found that—(1) The coccus isolated from the abscess, (2) the coccus isolated from the tooth, and (3) the coccus isolated from the sputum, were all agglutinated to the full titre by the serum of one of them and were identical antigenically. Moreover, all these were "perfect cocci" in the sense already mentioned.

This coccus was called type B.

The perfect type forms of the enterococcus (types A and B) are invariable in their sugar reactions, except perhaps with regard to saccharose, which does not seem to be a good differentiating sugar. When these cocci are freshly isolated they usually ferment saccharose, but after several months transplantation they may take a longer time to ferment this sugar or not ferment it all, but this quality seems to be resuscitated by passing the coccus through an animal fluid or by heating it and re-isolating it from the heated emulsion.

All perfect forms of the enterococcus, either type A or type B, are agglutinated to the full titre by the corresponding serum. Perfect forms of type A are much commoner than perfect forms of type B.

Dr. Haslett has shown that these two types produce during their growth a substance similar in nature to the soluble specific substance isolated from the pneumococci, and that these substances determine the specific types of the organism.

All liquefying enterococci are not perfect forms, as some strains deposit rapidly in glucose broth, and these granulate when boiled; some of these at least have been shown *not* to produce the soluble specific substance. Such strains may or may not agglutinate properly.

All enterococci which do not liquefy gelatine deposit rapidly in two per cent. glucose broth, that is, they are acid sensitive and as a rule granulate on boiling, i.e., are heat-sensitive. In other words, they may be regarded as rough forms of the type organism. All enterococci that have abnormal sugar reactions, i.e., that depart from the constant sugar reactions of the type forms, possess also these two properties—they are acid-sensitive and heat-sensitive. Thus the non-mannite

fermenters, the raffinose fermenters, and the rare inulin fermenters appear always to be heat-sensitive and acid-sensitive strains : at least up to the present we have not found any exception to this rule.

The agglutination of the 'rough' forms with the type specific sera is very varied. The rule is that the majority of the strains investigated agglutinate to some extent with one or both of the type sera. A few agglutinate to a much lower degree with one of the type sera. A few of the very rough forms may not agglutinate at all or may be thrown down by all three sera.

This scheme of classification has much to recommend it, and so many strains fit into the mosaic that we have little doubt that it will prove to be the natural and only possible classification of the enterococci.

Many interesting observations on the antigenic analysis of different strains of these cocci have been made by Dr. John Campbell and Dr. Haslett. These results on broad lines confirm the statements that have been detailed above. They show that type A coccus is much the purest antigenic strain and produces much the largest quantity of soluble specific substance, while type B produces a smaller quantity of soluble specific substance distinct from type A, but a larger amount of the non-specific factor; while type C seems to produce no soluble specific substance and has more of the non-specific factor.

Dr. Haslett will soon, we hope, publish the details of his research.

The non-mannite fermenting enterococci, however, need separate consideration, and introduce a subject of great importance and great difficulty in the study of this class of micro-organisms. We are quite satisfied that Dible is correct in classifying such strains as true enterococci. This form of enterococcus frequently occurs in the tonsil and in cases of bowel disturbances, such as ulcerative colitis. If a sample of mucus from a case of ulcerative colitis be grown in broth and heated to kill off the coli, and then planted on a mannite Conradi plate, a great number of cocci may be found that do not seem to ferment the mannite—if these are picked off, some will be found to ferment mannite in a day, others two, three, four, five, or seven days, and others may not ferment mannite at all. These are all heat-resistant cocci, and usually grow in bile in chains, that is, they give the characteristic tests for enterococci. We find, however, that those that fail to ferment mannite are less heat-resistant than typical mannite fermenters. They usually withstand heat at 56° for an hour, or at 60° for half an hour, while any further exposure will probably kill such strains. The mannite fermenters will often survive a much longer exposure at these temperatures. These non-mannite fermenters generally grow in bile in long chains, but with some strains this test is not so satisfactory. Antigenically, they are only agglutinated in the lower dilutions by the type sera—some may not be agglutinated at all. With several such strains that did not at first ferment mannite, Dr. Haslett and I have succeeded in making them ferment this substance, and in such cases the mannite fermenting variant had a greater tendency to agglutinate with the type sera. In fact, we believe that there are strains that show a gradual transition from the typical mannite fermenters to those that do not ferment mannite

at all. We now believe that these transitional forms are the result of 'phage' action. It is this type of coccus that Bargen has described as the cause of ulcerative colitis, and we believe this non-mannite fermenting diplococcus is simply a 'phage'-infected enterococci or a permanent mutant, the result of 'phage'-infection. We have on several occasions isolated a 'phage' from cases of ulcerative colitis, to which the type forms of the enterococcus are sensitive.

Almost a year ago we had occasion to study the coccus isolated from a case of ulcerative endocarditis, and we were struck with its resemblance to these non-mannite fermenting enterococci. It grew in a similar way on Conradi Drigalske's medium and on chocolate, though on this medium it gave a definite green colony and would therefore be classed as a viridans streptococcus. It grew well on glucose broth, rapidly depositing, and only produced a fine opalescent growth on Douglas broth. It did not ferment mannite or lactose, but fermented saccharose, salicin, raffinose, and inulin. It did not coagulate milk nor liquefy gelatine. It did not give the heat test or growth-in-bile test satisfactorily. Microscopically, it was an ovoid coccus and showed bacillary forms. After transplanting it for a month I laid it aside, but before throwing it away I again planted the cultures out and found that one of the culture tubes did not produce the green coccus, but a typical liquefying enterococcus. This might have been the result of accidental contamination, but I did not think this was the correct explanation, because the same thing had occurred before with a viridans culture from a gall-bladder which had been subcultured for four weeks, always as a viridans coccus. This culture had been left in the incubator for almost a month, but when transplanted at the end of this time turned out to be a liquefying enterococcus. I also had the same experience with a viridans culture from the root canal of a tooth. This broth culture had been planted from a single viridans colony into Douglas broth, and had remained in a broth tube in the fine growth, which I have described, for several weeks. I noticed the growth was thicker than it had been, and when it was planted a typical enterococcus grew.

Because of these experiences I determined to make a systematic study of the next case of ulcerative endocarditis that turned up in the laboratory. This was a case of Professor Thomson's, and was clinically a typical case of the disease. The same viridans coccus had been isolated three times by different observers. This coccus was at first difficult to grow, and did not appear in the culture flasks until the third day. From the first blood-agar plate it was transplanted with difficulty from single colonies, but after several transfers in glucose broth it grew well, forming a rapid deposit. On Douglas broth it grew in a fine opalescent growth barely perceptible, and was finely granular or flaky when examined with a lens. It was transplanted on to Conradi and chocolate, and grew with a markedly mutant growth, and on chocolate with a vivid green colony that gave the iodine reaction as a central dot in all the colonies. Thinking the mutant character on Conradi might mean a mixed culture, I transplanted several times from separate colonies, but always obtained the same mutant growth. On planting the coccus on moist agar I obtained many worm-eaten colonies, and thought there might be evidence of 'phage'-infection. This coccus gave the following sugar fermentation :—It did not ferment mannite

or lactose, but fermented saccharose, salicin, glucose, and inulin. It did not grow in bile, and stood heat for almost an hour at 55°. I kept the broth cultures of this coccus and heated some of them, and at the same time kept the green coccus alive by frequent transplantations from glucose broth to glucose broth. A glucose broth culture was always dead in three days, but the coccus lived in Douglas broth for four or five weeks or longer. I noted that some of the broth tubes became thicker, and when planted out grew either a pure enterococcus or in some cases an enterococcus and a viridans colony. If such mixed cultures were left longer or transplanted into another broth tube, nothing but enterococci colonies developed. I also noted that in one of the mixed cultures the green colonies nearly all developed numerous daughter colonies, and the next day this broth produced nothing but colonies of enterococci. After planting again from single green colonies and getting a similar result, I came to the conclusion that the green colony had reverted to an enterococcus and must have been 'phage'-infected.

These observations were repeated again and again with the same green coccus, which has now been kept growing for almost a year. These reversions did not always occur, but we found the following procedures were apt to determine a reversion :—

(1) Rapid transfers from glucose to glucose;

(2) Heating the broth cultures at 55° for almost one hour;

(3) Treating the culture with dilute iodine;

(4) Fishing out daughter colonies and replanting these;

(5) Growing the culture in blood.

This coccus has been kept alive for about a year, and reversions still take place, though they do not occur so frequently as they did at first. This corresponds with D'Herelle's observation that the longer the coccus has lived in symbiosis with the 'phage' the more difficult it may be to obtain a reversion. I am quite aware that a phenomenon of this nature needs the fullest confirmation before it can be accepted, and I hope to find better and more certain methods of causing 'reversions' of such cocci, as I am convinced that 'phage'-infection of the coccus is the true explanation of these results.

My reasons are as follows :—

(1) The character of the coccus and its method of growth on fluid media.

(2) The mutant character of the coccus, especially on media such as C.D.

(3) The fact that the colony seems very frequently to produce daughter colonies —a normal enterococcus does not produce daughter colonies.

(4) The character of the growth on moist agar.

(5) The presence of the iodine reaction. I have come to believe that, with enterococci at least, this reaction is an indication of 'phage' reaction.

(6) The inulin reaction with all such cocci I also believe will be found in the case of the enterococcus to mean 'phage'-infection.

(7) The microscopic appearance of these cocci suggests that they are enterococci.

(8) The fact that reversions were obtained many times.

The next case of ulcerative endocarditis was one of Dr. Marshall's. It ran a rapid course to a fatal termination, and might perhaps rather be classified as a case of malignant endocarditis than a case of subacute ulcerative endocarditis. I told Dr. Green to culture this case with the greatest care.

He took four flasks; two contained Douglas broth and two contained glucose broth, and all four were inoculated with about 2 c.c. of the patient's blood. All four flasks were incubated for five days without being touched. On the fifth day one of the glucose flasks was seen to be changing colour, and a film was made with a platinum loop, stained, and examined. A streptococcus was found growing in dense clumps with long chains. Another film was examined on the following day, and now the streptococcus was seen to be growing diffusely through the film, but still with marked chain formation. On the following day the film was quite typical of enterococcus growth in blood, and this the coccus proved to be on further examination. It was a typical type A liquefying enterococcus. The same sequence of events was followed in one of the broth flasks, which did not become discoloured till the ninth day, and on this day a culture was made on blood agar and chocolate. The coccus thus obtained grew in a fine irregular way on chocolate, and produced the peculiar colony which we now call the paraffin colony. On chocolate it looks as if little irregular clumps of solid paraffin had been put on the medium. This appearance is exactly the manner in which one of Birhaug's strains grows on chocolate. This also gave an intense iodine reaction involving the whole colony. This colony has been transplanted frequently from glucose to glucose, etc., and is still alive, but after some months it has grown more regularly in broth, and has now become a similar colony to the Madden coccus, though it still gives an iodine reaction. From this coccus numerous reversions to a typical enterococci have also been obtained.

From a study of this coccus and its reversion in the blood-culture flask, we believe that growth in blood may prove an effective method for causing reversion of these 'phage'-infected cocci.

A culture from a fourth case of ulcerative endocarditis was also obtained, and was found to give a similar growth on chocolate and also gave the iodine reaction. This case was only studied imperfectly, but Dr. Green obtained an enterococcus from one of the broth cultures of this coccus.

In order to confirm the view that these cocci were 'phage'-infected, the Morrison type I coccus was artificially infected with a 'phage' to which it was sensitive, and after secondary cultures had appeared these were planted on mannite C.D., and some of the 'flatter-formen' colonies were picked off and transplanted on to glucose broth and then again planted on mannite, always picking off the aberrant colonies that did not ferment the mannite—in the end, cultures were obtained that grew in the same way as the Madden and Connor cocci. The Morrison 'phage'-infected coccus gave the following reactions. It did not ferment mannite or lactose, but fermented glucose, salicin, raffinose, and inulin. It did not coagulate milk or liquefy

gelatin or grow in bile, and its growth in broth was exactly similar to that of the Madden coccus. It grew on C.D. with mutant colonies, and on chocolate with a green colony, giving the iodine reaction identical with the Madden coccus. It also produced daughter colonies, and frequent reversions were obtained to a normal enterococcus—in fact, it behaved in every way as the Madden and Connor cocci had done.

We now find when our attention has been directed to this phenomenon of 'phage'-infection that it is not an isolated finding, but one of very common occurrence. As you are aware, quite a number of monographs and papers have been written on chronic onychia which so commonly occurs in women, and not one of these students of this skin condition, with the exception of Doctor McCaw, has ever noted the constant presence of enterococci in the affected nail wall of this disease; yet in Belfast this coccus can be isolated in every case where the attempt is carefully made. What is the reason of this? We have used here the capillary method of cultivation, and this method owes its efficiency to the fact that it tends to weaken the 'phage' and allows the infecting coccus to revert. If the onychia be cultured in the ordinary way by making a broth-emulsion of the muco-pus from under the nail wall, and this be planted on chocolate plates, it will be found that many or all of the enterococci and coli give the iodine reaction, and the enterococci colonies when planted out may not grow at all or may grow with great difficulty, and when we do get a successful growth we shall find that these cocci have the characters and methods of growth which have been already described as characteristic of 'phage'-infected enterococci. The same thing has frequently happened with cultures from the tonsil and from other sources. For instance, the usual plan of isolating the enterococcus from the tonsil or other focus, where it is certainly mixed with other organisms, is as follows: The swab is thickly planted on broth and allowed to incubate overnight. The mixed growth is heated at 56° for one hour, and then some fresh broth is added, and after a further incubation is planted on a C.D. plate—frequently a pure culture of enterococcus is thus obtained. On many occasions, however, no growth has resulted from this procedure, but on incubating the tube for two or three days longer, a growth of enterococci may be obtained. The reason is that the enterococcus in the tonsil is frequently 'phage'-infected, and in the culture tube the associated micro-organism, living or dead, tends to weaken the 'phage' and allow the enterococcus to grow out. This can easily be shown to be the correct explanation by planting out the throat-swab thinly on chocolate plates and testing the colonies for the iodine reaction. Such colonies, if picked off and separately grown, will behave as the other colonies described. From a study of numerous septic foci, I am coming to the conclusion that infection with the enterococcus generally means an infection with a coccus living in symbiosis with the 'phage,' or, expressed in other terms, the enterococcus is the "carrier of a virus."

It has been shown that from the septic foci of many rheumatic patients the enterococcus can be isolated, and if, as has been shown, the coccus frequently occurs in the 'phage'-infected state, this condition may make its isolation very difficult. The correct conception of the septic focus is not that it is to be regarded as the

cause of a rheumatic condition. Rheumatism is a general, not a local, disease, but owing to the nature of these septic foci, they may provide a breeding-ground for the virus of the disease. If this view is correct, we can see how an acute infection of the tonsil with a hæmolytic streptococcus or other active infection may destroy the restraining 'phage,' and set free the coccus in a more infective form.

One of the great difficulties that the interpretation of finding the enterococcus in septic foci has presented, has been explained by the fact that the coccus is frequently 'phage'-infected. Supposing, for instance, an enterococcus is isolated from onychia, and the patient has septic teeth or septic tonsils, it is frequently found that an enterococcus may also be isolated from the tonsil or the teeth, but the cocci so isolated may have different biological and antigenic reactions—one may be a liquefying form, another a non-liquefying form, and a third a non-mannite fermenter. Have we a right to draw any inference from this?

In Mrs. Morrison's case we obtained an enterococcus from her blood, two from her tonsils, and nine or ten colonies were picked off from the plate planted from her septic tooth. These were all tested out and found to be true enterococci, but one only of these thirteen strains proved to be a typical type I liquefying enterococcus; the others proved to be non-liquefying strains. Her blood agglutinated well the type I coccus, but only imperfectly the other strains from her tonsil and blood which were tested. These were slightly granular, so that the agglutination was doubtful.

In the case of Miss McMaster, a typical type I coccus was obtained from her blood, a non-liquefying form from her tonsil; two rough strains were also obtained from two onychias that developed during her acute illness. Her sputum was injected into three mice—none of these died from pneumococcus septicæmia, but one of them died on the tenth day, and a liquefying enterococcus was isolated from its heart blood. Her blood agglutinated the type I enterococcus definitely.

In a case of typhoid fever where the typhoid bacillus is isolated from the blood, fæces, urine, etc., we expect to find the organism give the typical biological and serological reactions of the bacillus typhosus, and if it did not there would be a doubt as to its identity. This rule, however, is not absolute, and it is now known that inagglutinable and non-motile forms of the bacillus typhosus may sometimes be isolated from cases of typhoid fever, and in the 'carrier state' rough forms of the typhoid bacillus are known to occur. A similar condition of affairs occurs in dysentry and cholera, where inagglutinable and atypical forms of the infecting organism may occur. The probability is that these atypical forms are the result of 'phage'-infection.

If the enterococci in these septic foci are 'phage'-infected, this would naturally account for the different antigenic and different biological forms found in the same and in different foci. An interesting point arises with regard to such infected patients—if the serum of these patients gives an agglutination with the enterococcus, it is usual for the specific form of the coccus to give a better and more definite agglutination than the altered form found in the lesion.

From the number of different strains of enterococci isolated from septic foci, it seems a likely explanation that the coccus was varying in the infected focus.

Usually in one infected focus the strains isolated were identical, but there were many exceptions to this rule; also, the enterococci isolated from different foci of the same patient were quite often different—antigenically and biologically. Again, from the same patient at one time a liquefying enterococcus might be isolated, and at another time a non-liquefying form. For five years an endeavour was made to find an explanation of these variants by trying the numerous expedients that are credited with producing bacterial variation. Although a great deal of work was expended on this research by Dr. John Campbell, Dr. Haslett, and myself, it may be said that these attempts proved almost a complete failure. Dealing with the type forms of the organism, we were quite unable to get any definite and permanent variation. As I have already pointed out, Dr. Haslett and I had a certain amount of success with some non-mannite fermenting strains, but it now seems quite probable that these strains may have been 'phage'-infected. We are glad now to know, after these arduous endeavours, that D'Herelle, Flue, Burnett, and others contend that there are certain strains of all organisms that cannot be changed by such expedients, and that from these strains the 'phage' cannot be isolated. These are the ultra-pure strains of D'Herelle or the indicator strains of Burnett. But the case is very different if we infect these strains artificially with 'phage'—then we can usually get mutations comparatively easily. Thus by infecting type I and type II enterococci with 'phages' to which they were sensitive, we have obtained numerous mutations: enterococci that do not liquefy gelatine, inagglutinable forms, forms that agglutinate differently from the original strains, forms that do not ferment mannite, etc. In fact, all the different forms that are obtained from various sources can be obtained by the action of the 'phage' on the typical type forms. It may be added that all the work that has been done in Belfast tends to support the conception of D'Herelle—that the 'bacteriophage' is the most important factor in causing mutations of this type of micro-organism.

But whither does all this lead us and what is its relation to the rheumatic problem? Is this a jumble of undigested data, or is it a reasonable hypothesis?

To the evidence that has accumulated since the days of Thiercelin I should like to add—

(1) We have found that the enterococcus usually occurs in a septic focus in a 'phage'-infected form. That the probable reason it can be isolated from such foci is that the 'phage' is weakened by the associated micro-organisms and by the special methods used for its isolation.

(2) The same reasoning might show the difficulty of isolating this 'phage'-infected coccus from the blood or joints where there are no associated micro-organisms, and in the few cases where it has been isolated would explain the length of time that it has taken to grow out and the special methods required for its isolation. Arloing, Langerou, and Semple have reported that red cells freed from plasma may completely absorb the bacteriophage corpuscles, and it is stated that this also occurs with certain other viruses.

(3) This 'phage'-infection would also explain why when a streptococcus has been isolated it may grow out in different antigenic and biological forms. At one time the

coccus of Clawson, at another the coccus of Small or Birhaug, or even the atypical streptococcus described by Cecil, Nicholls, and Stainsby, or to go into past history, the diplococcus of Poynton and Payne and Beattie.

(4) In much of the recent bacteriological findings it is a streptococcus viridans or alpha streptococcus that has been incriminated as the bacterial cause of rheumatic disease, and we believe that a very large number of strains of streptococcus viridans are masked forms of the enterococcus—so that this evidence, as far as it goes, does not necessarily exclude the possibility that there may still be a specific rheumococcus.

(5) Cocci like Bargen's coccus, Small's coccus, and Birhaug's coccus, which have been fully described and can be obtained from the National Collection of Type Cultures, are all the type of cocci that suggest that they may be 'phage'-infected, or mutants the result of 'phage'-infection.

(6) Working with viridans cultures that first give the iodine reaction, we have isolated forms that exactly correspond to the cocci of Bargen, Small, and Birhaug.

This is merely a preliminary sketch of the views I have provisionally arrived at from a study of the enterococcus for many years. It is a theory that would account for many of the vagaries and difficulties of the rheumatic problem, and would allow us still to believe that there may be a specific virus for rheumatism, and that it cannot be adequately explained on a pure sensitization hypothesis.

Whatever fate awaits this theory, I feel sure that its confirmation or refutation will add to our knowledge of the mysteries of Bacteriology.

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The Red-Cell Sedimentation Rate of the Blood in Rheumatism and Arthritis

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HISTORICAL.

IF the coagulation of blood be prevented, the red cells will sediment, at first rapidly and then more slowly, finally forming a semi-fluid deposit overlaid by clear plasma. Under standard conditions, the rate at which this sedimentation takes place in the blood obtained from normal healthy subjects is surprisingly constant. It is, however, markedly altered by the presence of certain diseases.

These facts were originally noted by Biernacki about the year 1893, but no particular attention was paid to them until about twenty-five years later, when their importance in general medicine was pointed out by Fähræus, and then Westergren.

GENERAL.

The rate at which sedimentation of the red cells takes place seems to depend on the percentages of globulin and fibrinogen, and to a lesser extent lipoids, in the plasma. It is increased by processes giving rise to protein disintegration, in inflammatory and, above all, exudative processes—for example, infectious fevers, exudative pulmonary tuberculosis, acute and chronic arthritis—pregnancy, cancer, and nephrosis. Even slight infection of an acute type increases the rate, and in considering its significance in any particular case, care must be taken to rule out the possibility of even a cold or sore throat. Fähræus has found that the rate is increased in obesity: in surgical tuberculosis and chronic bone infection, such as osteomyelitis, there is generally a moderate increase: following a hæmorrhage high figures are often obtained. The rate is not affected by food or menstruation, nor do chronic conditions such as simple affections of the stomach and intestines, nervous and endocrine diseases, alter it.

METHOD.

The study of the subject was, and still is, greatly hindered by the variety of techniques used and the consequent difficulty, or impossibility, of comparison of different series of results. One of the most satisfactory is that used by Westergren. For the test he uses blood to which a quarter of its volume of 3.7 per cent. sodium citrate has been added as an anti-coagulant. This strength of citrate is isotonic, producing no laking of the red cells, and the amount is sufficient to combine with all the calcium present in the proportion of blood. The mixture is drawn up into a tube 2.5 mm. in internal diameter and 300 mm. in length, the lower two-thirds of which is graduated in mm. reading from above down. When the upper surface of the blood-citrate mixture has been brought to the zero mark, the tube is held in a

vertical position, the lower opening being sealed by pressing the point down on a rubber surface. The height of the clear supernatant column left by the sedimentation of the red cells is read at one, two, and twenty-four hours.

The test must be carried out immediately on the blood being taken, otherwise the rate of sedimentation may be markedly diminished.

Normal Figures.

In a series of observations, Forestier found that the figures given by normal people were as follows :—

	Men.	*Women and Children.*
1 hour	3—5 mm.	6—8 mm.
2 hours	10—12 mm.	12—15 mm.
24 hours	30—50 mm.	

Kahlmeter, working in Stockholm, allows up to 7 mm. for men and 11 mm. for women in the first hour as normal, and in my experience these are much nearer the figures generally found.

Rheumatism and Arthritis.

From the standpoint of sedimentation rates, it is convenient to divide the mass of conditions coming under the wide terms of rheumatism and arthritis into rough groups as follows :—

(a) *Acute:* 1. Acute rheumatism.
2. Acute infective arthritis (gonococcal, staphylococcal, etc.).

(b) *Chronic:* 1. Neuritis and fibrocytis.
2. Chronic osteo-arthritis.
3. Chronic rheumatoid arthritis (atrophic).

In acute rheumatism and acute infective arthritis the figures are usually very high, often 100 mm. or over for the first hour. As recovery takes place the rate rapidly falls, but there is generally some lag behind the clinical improvement. Recovery in acute rheumatism should not be assumed, or physiotherapy commenced, until the figures for the test are normal, otherwise relapses are liable to occur.

Neuritis and fibrocytis—sciatica, lumbago, etc.—generally produce no change. Coste and Forestier found only twenty-two per cent. give figures greater than 10 mm. in the first hour, and of these none exceeded 20. If a case of this kind show a rate of over 30 mm., the possibility of some other diagnosis being the correct one should be carefully considered.

Chronic osteo-arthritis has long been regarded as one of the most difficult conditions to treat with any degree of success. It appears to be largely degenerative in nature, and it usually attacks one or two of the large joints of an aged subject. Lipping of the joint surfaces and osteophytes are sometimes present. Many regard the process as absolutely non-infective, and this view is borne out by sedimentation-rate determinations on sufferers from the disease. Kahlmeter states that the figure is invariably normal. Forestier found that sixty-two per cent. were under 10 mm.,

while a further thirty per cent. lay between 10 and 20 mm. Oppel, Myers, and Keefer of Harvard, using a different technique, agree with Forestier, and are of opinion that there are many exceptions to the general rule. They did not, however, obtain a very high figure in any case of the condition.

Next to pulmonary tuberculosis it is in chronic rheumatoid arthritis that the red-cell sedimentation rate is of greatest interest. In an active phase of the disease the figures are generally fairly high—50 or 60 mm. in the first hour and always over 20 mm. The values run fairly well parallel with the course of the disease, increasing when it becomes more active and falling with quiescence. Thus, by observing the curve, the progress of the disease may be observed and the effect of different treatments evaluated. The curve of the sedimentation rate in a case of rheumatoid arthritis may be as interesting to follow as that of the sigma-reading in syphilis or of the blood urea in azotæmic nephritis. Wendell, Stainsby, and Nicholls found that the increase in sedimentation rate ran very closely parallel to the degree of joint involvement, and in an analysis of almost six hundred cases concluded that it is "a reliable criterion of the activity, or severity, of the arthritic process at the time of testing."

Rheumatoid arthritis has received more than its share of ill-conceived treatments, and it may be that the sedimentation rate will provide an easy means of correctly estimating the value of such procedures.

Following the enthusiastic reports of Forestier on the results obtained by the injection of gold salts, there has been a great vogue for this method. Some years must elapse before any considered opinion can be given, but it would seem that the treatment may be of value in many cases. Forestier is of opinion that it is not likely to be beneficial if the sedimentation rate be not increased, and checks the results of treatment by systematic determinations, altering the exact salt used if no decrease be produced. It is useful to have some means of selecting suitable cases, in view of the tedious and slightly expensive nature of the treatment. In the same way the effect of vaccine treatment may also be determined. Vaccine and gold salt therapy may often be combined with advantage, noticeable clinical improvement often taking place, even in severe cases, accompanied by a diminution in the sedimentation rate.

REVIEW

THE NEW ART OF LOVE. By G. R. Scott, F.Ph.S., F.Z.S. London: John Bale, Sons & Danielsson. 1934. pp. 114. Price 3s. 6d. net.

RECENT years have seen the publication of numerous books pertaining to sex, many of which had better never been written. Others have, perhaps, been of service when written by experienced medical practitioners. "The New Art of Love" has been written by a layman, and thus lacks the essential background of medical knowledge, and as a result is composed of little else except vague generalities of human sex life. It attempts to discuss such subjects as Marriage, the Choice of a Partner, the Honeymoon, Intercourse, Birth Control, Impotence, etc., in a manner suitable for lay readers, but whether anyone, even the most ignorant, would derive any benefit from its perusal is a matter of great doubt. Sir Arbuthnot Lane has written a foreword to it of twelve short lines, in which he says he has read the book "with very great interest and pleasure."

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Enterococcus and Sydenham's Chorea

By H. Hilton Stewart, M.D., M.R.C.P.Lond.,
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If one examines the literature on the bacteriology of chorea, one finds that as far back as 1894 a diplococcus was isolated by Dana from the brain of a fatal case. Since then many observers such as Triboulet, Croyon (1897), Westphal, Wassermann, Malkoff, Poynton and Paine (1901-3), Beattie,[1] and others have isolated different cocci as being the cause of rheumatic infection, and some have injected streptococci into rabbits and produced choreiform conditions.

In a paper published elsewhere in this Journal,[2] Sir Thomas Houston draws attention to the rôle of the enterococcus or streptococcus fæcalis, and its relation to rheumatism. He has endeavoured to correlate his work with the findings of other observers, and suggests that all recorded varieties of cocci may be enterococci living in symbiosis with a virus or 'phage.' For example, the coccus of Beattie gives all essential characteristics of an enterococcus. Sir Thomas Houston's experiments also show that some varieties of streptococcus viridans may be a 'phage'-infected enterococcus; his own words on this point are important. He says that his 'phage'-infection "would explain why, when the streptococcus has been isolated, it may grow out in different antigenic and biological forms, at one time the coccus of Clawson, at another time the coccus of Small or Birhaug, or even the atypical streptococcus described by Cecil, Nicholls, or Stainsby, or, to go into past history, the diplococcus of Poynton and Paine and Beattie."

One of his co-workers (Haslett), working with the three types of enterococcus A, B, and C, has found that the first two types produce a soluble specific substance. Type A is the purest form, and makes a fine emulsion. Type B does not contain so much specific soluble substance, and is not so good in emulsion; while Type C has no specific soluble substance at all.

It has been the custom for the last five or six years in the laboratory of the Royal Victoria Hospital to do agglutination tests with these cocci in many rheumatic conditions, chiefly of a chronic nature. A great number of these gave an agglutination, while cases which appeared to be normal controls did not give this reaction. These results have not as yet been published.

If one accepts the view that Sydenham's chorea is rheumatic in origin, and that the pathology is "a diffuse or disseminated encephalitis affecting chiefly the corpus striatum and involving the cortex and pia arachnoid,"[3] it occurred to me that one might get agglutination of the blood-serum from choreic cases to the organism responsible.

The findings, therefore, I wish to place on record are the results of agglutination tests from twenty-six cases of chorea, using the enterococcus as an antigen.

The dilutions of the enterococcal emulsion used were $\frac{1}{12.5}$, $\frac{1}{25}$, $\frac{1}{62.5}$, $\frac{1}{125}$.

As type A enterococcus forms a good emulsion, any agglutination in one tube or more was regarded as a positive; but as type B does not form such a fine emulsion, some spontaneous agglutination may occur in the first tube. It was therefore decided

that agglutination to type B must occur in two tubes or more if it was to be regarded as positive.

The results were as follows :—

Number of cases agglutinating type A -	17
Number of cases agglutinating type B -	7
Number of negative cases - - - -	2

Some of the positive cases were positive to types A and B.

An interesting point in regard to these agglutinations was that in the early cases no agglutination or only slight agglutination may be found, but as the disease progresses the titre rises, and in the chronic stage a fairly high titre may be expected. This may account for these two negative cases. In some cases the agglutination begins to fall after convalescence, but this is by no means the rule, and agglutination may be found for a long time. This is not to be wondered at when one bears in mind the frequency of recurrent chorea and, indeed, of rheumatic manifestations in general.

I attempted to pick out a number of control cases to compare results. Owing to the prevalence of the enterococcus in the various potential foci of infection in the body, the choosing was difficult. I took as a standard that the control cases must be (1) children, (2) without history of rheumatism, (3) with no history of scarlet fever or tonsillitis and whose tonsils and heart were normal, (4) without disease connected with the colon, such as appendicitis, diarrhœa, etc.

The following twenty-six cases were chosen :—Fractures, 8 cases; club feet, 8; splastic diplegia, 1; hernia, 3; œsophageal obstruction, 1; burns, 1; abdominal injury 1; cleft palate 1; cyst of neck, 1; cyst of ankle, 1.

I found that agglutination took place slightly in one case of this series of controls. All the others were quite negative.

These enterococcal agglutinations in chorea are put forward as a link in the "rheumatic chain." They certainly tend to support Sir Thomas Houston's views as to the rôle of the enterococcus in rheumatic infections. A large field of speculation is opened up. Can one foretell the likelihood of another attack of chorea by the titre of the agglutination? What therapeutic value will enterococcal vaccines have in chorea?

I have not as yet tried any therapeutic measures with either enterococcal serum or vaccine. My attempt has been solely to try to establish a connection between the enterococcus and Sydenham's chorea.

I have to thank Sir Thomas Houston and Dr. W. F. Green, to whom I am indebted for performing these agglutination tests.

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Electro-Cardiographic Changes in Rheumatism

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THE baneful influence of rheumatic processes on cardiac function has always been recognized as of paramount importance. Cardiac pathology is intimately concerned with the group of disease manifestations labelled 'acute rheumatism' or 'rheumatic fever.' It is an old observation that the more chronic varieties of rheumatism, comprising the groups of osteo-arthritis, chronic rheumatoid arthritis, and fibrositis, have no particular predatory effect upon cardiac structure or function. These ailments affect subjects of early or mature middle age, when abnormal cardiographic findings are likely to be coincidental rather than consequential to the chronic rheumatic condition. Acute rheumatism, on the other hand, shows its maximum age-incidence before the end of the second decade, and it has been truly said that this disease "licks the joints but bites the heart." It might reasonably be expected that cardiographic examination would enable us to trace with greater assurance the ravages of this dread disease on the virgin substance of the puerile or adolescent heart.

It is profitable to consider the limitations of the electro-cardiograph as a method of clinical research. The prime practical difficulty is that there is a good deal of variation in the curves obtained from large numbers of apparently healthy hearts. This fact is of importance when comparatively trivial changes in voltage or wave-form are found during the course of an acute rheumatic attack. Till recently, negativity of the T waves in lead 1 was considered to be of little import, but the statistical researches of Willius, MacIlwaine, and Boyd Campbell[1] showed that this abnormality was associated with an expectation of life so short as one year. Again, inversion of the T waves in lead 3 is often found in healthy hearts. Amongst elementary school children, percentages varying from twenty-five (Shookhoff[2]) to 54 (Perry[3]) showed T_3 inversion. Shookhoff and Taran found that the direction of the T wave in lead 3 changed from time to time in three out of twenty normal children. The complexity of the subject is further demonstrated by the work of Nishigiwi,[4] who found that an upright T_3 could be altered in size or direction by cardiographing patients in a "bent forward" position. Some observers are, however, beginning to doubt the complete innocuity of T_3 inversions. Marshall,[5] for example, in a recent study of rheumatic carditis in children, found inverted T_3 in a high proportion of his cases, and made the interesting observation that in some instances T_3 subsequently became upright as the clinical condition improved.

The electro-cardiographic method takes no account of etiological factors. A heart-block produced by diphtheria toxin will give similar tracings to one produced by gumma. It must also be confessed that normal records are sometimes given by seriously diseased hearts—probably because the conventional three leads give only a fragmentary picture of the myocardial function as a whole. The salutary con-

clusion can be drawn that electro-cardiographic evidence is of little value when divorced from clinical findings.

Within the past decade, cardiologists have interested themselves in the early cardiac manifestations of acute rheumatism. The comparatively insignificant phenomena of the acute phase as a rule respond readily to routine remedies, but the rheumatic process is apt to smoulder in the heart, and many cases require treatment of a length and seriousness comparable with that meted out to tuberculous subjects.

Early in the rheumatic attack tachycardia is a universal finding, but usually disappears after a few weeks' rest in bed. A persistently rapid heart should, however, be regarded as a damaged one. Occasionally paroxysmal tachycardia may be the cause, and in the absence of appropriate treatment, cardiac failure is likely to supervene. Intermittency of the pulse also calls for cardiographic investigation, as premature contractions would suggest the presence of myocardial inflammation. Intermittency is sometimes due to partial heart-block—conclusive evidence of myocardial mischief.

Cases are occasionally encountered of patients recently recovered from acute rheumatism who show high-grade partial or complete heart-block. Such patients have few or no cardiac symptoms beyond breathlessness on effort, general weakness, and lack of interest in life. Examination may show no abnormality of cardiac size or sounds, and in the presence of complete A-V block the pulse is regular, and often of normal frequency. An electro-cardiogram will, however, provide the key to the situation. Auricular fibrillation may be a complication of rheumatic fever, but this condition can usually be identified without recourse to graphic methods.

It is certain that these major perversions of rhythm occur with greater frequency than is generally appreciated, and inadequate treatment will surely result in much unnecessary cardiac invalidism.

Less obvious but equally informative changes in wave-form have lately been described in rheumatic carditis. Seaham[6] and his colleagues have drawn attention to the absence of an iso-electric period in the ventricular complexes of lead 2 as a definitely pathological finding. This is probably due to intraventricular block. Notching or prolongation of the QRS complexes in leads 1 and 2 arises from the same cause, but indicates a more extensive lesion. These partial heart-blocks are not, as a rule, significant of irreversible damage; given careful treatment, they frequently disappear, and herein lies the hopefulness and responsibility of the medical attendant. For the detection of such lesions electro-cardiography is essential, and the progress of the case should be followed by repeated examinations.

In established cardiac disability the electro-cardiogram will often confirm a doubtful diagnosis, and give valuable information regarding the reaction of the heart-muscle to the strain of valvular deformity or extra-cardiac adhesion. It is a matter of some difficulty to diagnose an early mitral stenosis. Such cases often show P (auricular) waves of increased amplitude, or they may be bifid. In the presence of gross mitral obstruction right-axis deviation is a prominent characteristic.

Myocardial insufficiency is the inevitable sequel of prolonged rheumatic activity

and mechanical embarrassment. The amount of damage can be roughly estimated by the extent of the abnormality of the cardiogram.

In conclusion, it may be said that electro-cardiography is useful in every stage of rheumatic disease. The most hopeful and least carefully explored field is that of acute rheumatism. Within the past few years minor but important degrees of cardiac damage have been recognized by the cardiographic method. It is thus possible to regulate the nature and duration of treatment in accordance with the needs of the particular case. In America, rheumatic clinics have done excellent work for many years, and the American Heart Association's methods of approach to the tremendous problem of cardiac rheumatism are an eloquent reproach to the medical profession and health authorities in these islands. The electro-cardiographic "follow up" forms an essential part of each clinic's activities. In this way much valuable knowledge is gleaned, and the benefit to the individual is incalculable.

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Spasm of the Colon

By WILLIAM LENNON, M.D.BELF., M.R.C.P.LOND.

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THIS is not a rare disorder; indeed, it is a common cause of chronic abdominal pain, and, according to some teachings, has a greater incidence than duodenal ulcer. Whether this be so or not, there is no doubt that it is still too infrequently diagnosed, and I have seen several sufferers who have had unnecessary and unavailing operations for other supposed conditions. Yet on clinical grounds alone it need not be difficult to make a diagnosis.

Colonic spasm has no apparent pathology, but is a disturbance in the nerve control of the bowel. At times the normal balance between constricting and relaxing influences is upset and spasm arises, with great diminution in the bowel lumen. So it may be singled out from the hazy conglomeration of conditions termed 'nervous dyspepsia.' Only a portion of the colon may be affected, most commonly the cæcal region, and transverse colon.

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Probably in every case the underlying element is the patient's nervous "make-up." They are highly strung, sensitive, nervous, and will describe themselves as such. It may therefore occur at any age, but the commonest incidence is between 20 and 40. The history is often of long duration, perhaps since childhood. One should be slow to diagnose its onset after the age of thirty-five. Naturally cases may occur in the same family. Of those I have seen the preponderance has been in males, although others mention an opposite finding.

The exciting causes are many—emotional stress, physical and mental overstrain are among the commonest—and the patient has usually appreciated this relationship. Cold, especially coldness of the extremities, may precipitate it. Certain foods, especially those with much roughage and seasoning, tobacco, and purgatives are other causes. In some cases the patient may incriminate one particular food, and there are some who believe that there may be an allergic factor causing this spasm, as in bronchial asthma.

The usual complaint is of abdominal pain or discomfort. Its situation is variable, although for the same patient it may be referred to a constant site. A common location is the cæcal region, and so a diagnosis of chronic appendicitis is an easy pitfall; or it may be referred along the transverse colon, suggesting duodenal or gall-bladder trouble. An important feature is the outlining of the pain by the patient; often he will delineate its extent along the colon with the edge of his hand. A patient with duodenal ulcer more often points with a finger to the painful area. The pain is usually dull and continuous, and may be very severe. A patient may be pale and agonized by its intensity. The duration is variable; it may be sustained for hours without diminution, and it relaxes slowly. Occasionally there is abrupt cessation. It seldom causes loss of sleep. There are not the sudden stabbing exacerbations which may occur in appendix trouble. There may be, too, a confusing history of food relationship, owing to the superimposed gastro-colic reflex. Rest and warmth may assist in the relief of pain, but alkalis are ineffectual.

Constipation—the so-called spastic constipation—may be of such a type that it assists in diagnosis. It tends to be variable. On some occasions the patient has normal evacuations; at other times, during spasm, constipation. Then the stools may be so attenuated in their passage through the narrowed spastic area that they appear like pencils or ribbons, or they may be fragmented. This is a simple diagnostic point of paramount importance, demonstrating as it does the actual lumen of the colon. One case which I encountered complained that the bowel never felt empty, presumably due to spasm of the rectum. Mucus may be present.

Other points in history are of lesser importance and may be confusing. During periods of spasm the severity of the pain may diminish appetite, and at any time superadded hypertonicity of the stomach may give rise to a sense of early repletion. Often there may be, too, superadded nervous symptoms indicative of the fundamental disorder. The patient may have times of freedom, perhaps even for months, and these remissions may again suggest duodenal ulcer, a condition where remissions have been too much stressed.

On examination, the patient often portrays his temperament—the spare, thin, restless, mentally alert type, perhaps substantiated by the increased reflexes and difficulty in muscular relaxation. But the important examination is that of the abdomen whilst the spasm is present. Then the affected area of colon may be plainly felt, like a short rubber bar, and running perpendicularly or transversely, according to its situation. As the patients are usually intelligent and inquiring, they not uncommonly have discovered its occasional presence for themselves. The palpable colon may or may not be tender. The variable presence of this sausage-shaped tumour is very diagnostic. One day it may be plainly felt, the following absent. And if the patient presents himself at a time of well-being, the abdominal examination will be negative.

Rectal examination may also show the spasmodic condition of the bowels, the walls fitting tightly around the examining finger. Sigmoidoscopy may also reveal this spasm.

X-ray examination will give final proof of the condition, the colon lumen in the affected area often appearing like a piece of cord. A meal is better than an enema, as the latter may relieve the spasm. It will be understood that X-ray will be negative during a remission.

In differential diagnosis it is most commonly confused with duodenal ulcer and chronic appendicitis. Certainly one should never diagnose chronic appendicitis without having considered this condition. Several points of similarity to ulcer have already been mentioned; amongst other distinctions, the occult blood-test is simple and useful.

As regards outlook, it is difficult to promise a cure, but by prophylactic and medical means one can greatly ameliorate these cases. It is probable, too, that if attacks of spasm can be overcome for a time, relapse is less likely, there being a degree of habit in its occurrence.

In treatment, the condition should be explained to the patient, and the absence of any organic disease stressed, as often the apprehension of some serious malady aggravates. The exciting factors, too, should be recounted, so that he may guard against them.

The patient's mode of living should be carefully inquired into, paying attention to such points as time and duration of meals, sleep, occupation, and domestic relationships, and any revision made which will put the patient's life on the best hygienic level.

The dietary need not be too much a hardship. Food should be as bland as possible. Thus milk, eggs, custards, jellies, thin white bread and butter, plain cakes, strained soups, fish and white meats, preferably boiled or stewed, are permissible. Vegetables should be sieved, and potato is best in puree.

Undesirable foods are roasted meats and game, raw fruits, especially under-ripe and seeded fruits, seeded jams, currants, condiments, strong tea and coffee. Alcohol and smoking should be reduced to a minimum. After food it is well to rest for a time, especially in recumbency.

Chilling of the feet and body should be avoided, and some patients are helped by a woollen abdominal binder. Warm baths are useful in relieving spasm.

Of drugs, those of the atropine group are of great service, tincture of belladonna or hyoscyamus being commonly employed. One must find the optimum dose for each case, as individual susceptibility is variable. It is best given before or between meals. Its use may be discontinued at times of well-being, but commencing constipation is a signal for its use.

If the pain be very severe, tincture of opium may be given with the belladonna, but its use should not be long continued. Liquor hydrargri perchloridi has been recommended, but its rationale is not obvious.

Only one laxative is permissible, and that is liquid paraffin. If necessary, it may be reinforced with magnesia. Vegetable laxatives must always be avoided, as they increase peristalsis. Enemata are not indicated, although sometimes a warm injection of four or five ounces of paraffin gives relief.

Such sedatives as bromides may seem indicated, but they are not very helpful, and so-called nerve tonics are usually to be avoided on account of the strychnia they contain.

Non-Union in Fractures

By A. H. Baker, M.D., F.R.C.S.ENG.
Consulting Surgeon, Hounslow Hospital

"Neither is it on the process, on the means, but rather on the result, that Nature in her doings is wont to trust us with insight and volition."—Carlyle.

In the days of the older and more picturesque bone pathology we used to visualize a fracture as setting free swarms of osteoblasts from imprisonment, which then wandered about among spicules of cartilage, depositing fibrous material, secreting osseous matter, and generally influencing the tissue fluids, and through them the blood, to part with calcium and phosphorus to aid them in their work. When they grew too large and fat they took on a destructive function and were known as osteoclasts. The osteoblast had indeed an important rôle, and this had an advantage, for blame for failure of union in a fracture was easy to assign. As stated by one textbook : "The want of union is evidently due to defective activity of the bone-forming cells in the vicinity of the fracture." After that it comes as rather a shock to find the categorical statement of two recent writers[1] that "adequate immobilization is the *only* factor of importance in establishing non-union." Unfortunately for our hopes of relegating responsibility in the matter, such one-time useful headings as "Age of the Patient," "Inadequate Blood-Supply to the Fractured Ends," "General Diseases, such as Syphilis," and now even "Local Suppuration," are likely to be deleted by a stroke of the blue pencil. It is forced on us that we must learn what we

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can of the process and of the means by which union is ordinarily obtained. It then becomes clear how comparatively simple are the factors determining failure.

The essential steps in the repair of a fracture are recognized to be formation of a hæmatoma between and around the fractured ends, organization of this hæmatoma to form granulation tissue, calcium deposition and irregular chondrification producing soft callus, ossification of this callus by ingrowth of blood-vessels, and, finally, transformation of callus into true bone with Haversian systems and typical arrangement of trabeculæ. Until the formation of clinically firm bone-callus is successfully accomplished, complete immobilization of the bone-ends in apposition is essential. Malunion there may be; refracture or bending at the site of repair may occur after that stage, but ultimate union is assured. Movement, even to quite an excessive degree, will not necessarily inhibit the appearance of the initial soft callus, but it will prevent *union* by callus. There is the story of the shipwrecked man with a fractured thigh who lived for many days with his leg swinging about in the waves. The femur showed a very exuberant callus around each end of the fracture, but there was no union. A pseudarthrosis was in process of formation. How may the intermediate steps fail that lead to the formation of bone-callus?

Recent observations on experimentally produced fractures in animals point to the importance of the hæmatoma. Not only does an actively organizing clot form a scaffolding through which the young fibrous tissue grows; it also acts as a medium for the deposition of calcium. W. J. Potts[2] concludes from his experiments that the clot may contain the enzyme phosphatase which initiates the chemical change occurring during the deposition of calcium. One of the most important actions of the hæmatoma is to strip up the periosteum from the bone-ends. The writings of Leriche and Policard,[3] and of D. M. Grieg[4] of the Edinburgh College of Surgeons, have materially altered our conceptions of the periosteum and of its function. Wherever periosteum remains attached to bone, it must be considered as limiting osteogenesis. Only when there is a more or less extensive stripping up of the periosteum at the site of a fracture can there be an exuberant callus. It is the occurrence of hæmorrhage around the fractured ends that causes this stripping, and where there is little damage to muscle—as in fractures of the shaft of the tibia where the bone is in large part subcutaneous—the comparatively small amount of hæmorrhage is associated with delayed union. The same result was obtained by Potts in experiments in which he carefully sponged out the blood-clot. Incidentally, this observation of Potts' is against aiming at too bloodless an operation in the case of plating or bone-grafting.

"Fibrous tissue has the property of arresting the extension of bone." This dictum of Leriche and Policard explains many points in the non-union of fractures. The neck of the femur is covered by fibrous bands known as retinacula, lying deep to the synovial membrane. Where these bands remain adherent to the fractured neck of the femur there can be no union by bone-callus. Moreover, these bands retain their vascularity, and thus can take no part in the process of de-differentiation which would render them ossifiable. They remain as fibrous tissue, and lack of impaction allows them to grow between the fractured ends, successfully blocking union between

the head and neck of the bone. It is probable that these subsynovial retinacula play quite an important part in preventing union in the neck of the femur. A fracture at this site is also characterized by the great difficulty in obtaining adequate immobilization between a large lower fragment on which gravity and muscular pull have full play and a small, upper, uncontrollable fragment.

Cellular organization occurs not only in the hæmatoma. At the same time as fibroblasts are invading the clot and young blood-vessels are growing in to convert it into granulation tissue, an important change is taking place in the bone, in the torn periosteum, and even in the muscle-fibres through which the clot has permeated. Hyperæmia causes a progressive decalcification of the fractured bone-ends. Hyperæmia and traumatic œdema combine to bring the various connective tissues into an embryonic state, to which the term 'de-differentiation' has been applied. In this embryonic transformation the decalcified bone-ends join. It is on the recognition that osteogenesis is only possible in connective tissues which have first undergone de-differentiation to an embryonic form, and that, granted an adequate supply of calcium—the "local calcific surcharge"—osteogenesis is then their natural line of development, that the "new bone pathology" rests. One factor can effectively prevent bone-formation, and this is conversion of the granulation tissue into fully developed fibrous tissue, because fibrous tissue, being relatively avascular, is unossifiable. A vascular blood-supply, local excess of calcium, and proliferated fibroblasts are what Grieg calls "the synthesis qualified for the production of new bone." Fibrous evolution of the interfragmentary connective tissue is absolutely fatal. Why does this fibrous evolution take place in a certain number of fractures?

In the initial soft callus formed on the fibrinous scaffolding of the blood-clot, there are represented three connective tissue elements, viz., chondroid tissue, fibroblasts, and a comparatively amorphic type of bone. If the bone-ends are in apposition and immobility is maintained, calcification proceeds, and bone is formed. If the bone-ends are separated and the fracture subjected to twisting and pulling strains, the interfragmentary tissue responds by the formation of fibrous tissue. There is always a race between the bony and fibrous evolution. There is also a limit to the gap that the fibroblasts can bridge, and if there is wide separation of the fragments, fixation by callus is delayed and fibrous tissue covers the bone-ends. Strictly limited movements of the shearing type will encourage the production of cartilage. In animals, on account of the difficulties of fixation of a fractured bone, chondrification of the callus tends to be marked. A *cartilaginous* pseudarthrosis is much more likely to occur in a fractured radius or ulna, where the degree of movement has been limited by the intact parallel bone, than in a femur or humerus. Surgeons accustomed to operating on bone for non-union will agree that fibrous pseudarthrosis is very much commoner than cartilaginous pseudarthrosis. Over-extension of fractures has become possible since the advent of skeletal traction, and I know that in at least one of my cases—a simple fracture of the femur, completely reduced and in perfect alignment—non-union was determined by over-extension. Young fibrous tissue will not grow across a fluid medium, nor will it cross muscle at right angles to its fibres. Encysting of the hæmatoma and transverse interposition

of muscle therefore act as insuperable barriers to union by callus. Union may also be delayed by excessive trauma to the periosteum and muscle.

Osteogenesis in fractures does not seem to be under the control of general calcium metabolism. It has been almost inevitable that the fashionable facts and theories of bone-growth should have been applied to repair of bone in fractures. But neither by parathyroid administration, nor by dosing with two quarts of milk a day, neither through the influence of ultra-violet light nor through the agency of vitamines A or D, has it been possible to effect the certainty or rapidity of union. It is a law of osteogenesis that the calcium used in bone-formation is obtained by bone-destruction. Its mobilization and subsequent fixation in bone repair are determined by a series of histological and chemical reactions initiated by the effect of trauma on the tissues around the fracture. Hyperæmic decalcification of the bones in the neighbourhood produces a local calcific surcharge. Without decalcification there can be no repair, and the healing bone can obtain its calcium only from the bones involved in the local hyperæmic reaction. If, as may happen in cases of delayed union, with the development of firm fibrous tissue in the fracture "scar," the bone-ends become eburnated and avascular, then immobilization of the calcium is rendered impossible. No amount of calcium, fed to the patient by mouth or intravenously, effects in any way the calcification of callus. From the point of view of prognosis it is of the greatest importance to interpret aright the X-ray findings in an ununited fracture. Decalcification of the bones is a sign of life and of active circulation; it is not a sign of atrophy. The dense shadow of well calcified bone, in the presence of a history even of slight mobility, should at once arouse suspicion of the presence of a pseudarthrosis. Despite the apparent mechanical advantage of firm, well calcified bone in the fixation of internal splinting, these are just the cases in which one learns to expect a poor result from open operation. If plates are used, there tends to develop a very localized patch of hyperæmia around each skrew, enough to loosen it. No reaction occurs at the fracture itself, and the plate either snaps across at about the time we are looking for union, or else the skrews work loose.

A great deal has still to be discovered about the physico-chemical processes determining the removal of calcium from the traumatized bone and its deposition in the callus. There is, for instance, no definite proof that the tissue fluids around the healing fracture are particularly rich in calcium. No very satisfactory means have yet been devized for studying the histological and chemical factors in conjunction. The treatment of compound fractures by open drainage and daily dressings, or continuous irrigation, is to be condemned on the grounds that it constantly removes the local excess of calcium. This method of treatment is also calculated to prolong the stage of hyperæmia; calcification does not occur until the blood-supply diminishes. Moreover, immobilization is very far from perfect when any form of dressing is a recurring incident in the treatment. Fibrous evolution of the connective tissue is thus encouraged. The rapidity of union of a highly infected compound fracture when treated by Winnet Orr's closed plaster method, with complete immobilization and no external interference, can be a source of considerable surprise when first observed. The first case I treated by this technique was a grossly septic

compound fracture of the tibia and fibula. When the plaster was removed at the end of four weeks, union was already well advanced, and it was quite firm and the patient able to leave hospital at the end of eight weeks. The temperature, which had been swinging up to 102° while the patient was on daily dressings and irrigation, settled at once after application of the plaster and never again rose above 99°. It also seems more than possible that the chemical action of the various antiseptics used in a wound may alter the physico-chemical reactions which determine the deposition of calcium, since these reactions are said to be controlled by the H. ion concentration.

The calcium needed in the repair of a fracture is not necessarily obtained only from the bone fractured. In certain cases neighbouring bones are also involved, both in the hyperæmia of trauma and in the relative hyperæmia of disuse, and show definite radiological evidence of decalcification. The carpus is a case in point. I think that one of the reasons why complete immobilization of the wrist is so successful in securing union in a fracture of the carpal scaphoid, is that it produces a partial decalcification of the whole carpus, and thus renders available a higher calcific surcharge.

So far, then, as we have been able to determine them, the essentials for rapid and firm bony union are :—

(1) The development of a hæmatoma, with coincident stripping of the periosteum.

(2) Apposition of the bone-ends without interposition of fluid or muscle.

(3) Complete immobilization to encourage the deposition of calcium as the hyperæmic reaction passes off, and to discourage the fibrous evolution of the inter-fragmentary connective tissue.

(4) Once clinically firm union has been obtained, controlled use of the limb, to correct the decalcification of disuse, and to promote the development of the late stages of ossification.

The chief faults commonly leading to non-union in fractures are too short a period of immobilization; incomplete fixation of the fracture; over-extension by the use of skeletal traction; frequent dressings and irrigation of compound fractures; and open operation with interference with the blood-clot and the insertion of foreign bodies.

And yet—to quote once more from that essay of Carlyle's—"Were defeat unknown, neither would victory be celebrated by songs of triumph."

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Rheumatoid Arthritis and Gold Salts Therapy

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IT is unfortunate that, in spite of the enormous amount of work that has been done in recent years on chronic arthritis, there is but little agreement as to what constitutes Rheumatoid Arthritis. Lawford Knaggs, in a report on the Strangeways Collection of rheumatoid joints in the museum of the Royal College of Surgeons, states that he was unprepared for the frequency with which some of the special features of osteo-arthritis were associated with others peculiar to rheumatoid arthritis. The difficulty of distinguishing osteo-arthritis from rheumatic lesions was such that two knee-joints from the same individual were separately diagnosed by an authority on the subject, one as being rheumatoid and the other as being osteo-arthritic in character.

The cause of rheumatoid arthritis is still unknown. The bulk of opinion in these countries is in favour of a low-grade non-specific infection. In France the tubercle bacillus is incriminated, but "rheumatisme tuberculeux" has never been accepted here. Workers in England and elsewhere, using Löwenstein's method, have failed to find tubercle bacilli in blood or exudates in polyarticular rheumatism.

The disease may occur at any age, but is most common between twenty and forty. Still's disease is probably rheumatoid arthritis modified by age, and there does not appear to be any good reason why the polyarthritis of women at the climacteric should not be considered as rheumatoid arthritis. A villous reaction may be evoked by infection or trauma as well as disordered metabolism. If chronic villous arthritis is due to endocrine dysfunction alone, one would expect that the condition would be much more common at the menopause. Sex is a predisposing factor, the frequency in females being four times that in males. The disease is said to be extremely rare in coloured races.

Mental strain and debility predispose to the disease. Dental caries, pyorrhœa alveolaris, septic conditions of the nose, ear, and throat, tonsils, pelvic diseases and intestinal auto-infections, are among the conditions which are said to act as infecting foci.

The morbid changes in the joints consist of swelling and hyperæmia of the synovial membranes, which may show marked proliferation. The fluid in the joint is slightly turbid from the presence of small fibrous deposits and leucocytes. The capsule of the joint becomes thickened, and degeneration with replacement by fibrous tissue takes place in the auricular cartilage and bone. J. F. Mackenzie describes changes in the bone-marrow of long bones. This appears to be similar to *gelatinous degeneration,* a condition which is sometimes found in starvation, phthisis, and other chronic diseases.

The onset may be acute, subacute, or chronic. In the first form the condition may closely resemble acute rheumatism, but the disease resists the salicylates, and soon the joints assume the typical characteristics. In the subacute form the joints show

slight swellings at first, and later the condition assumes the chronic form. The chronic variety begins insidiously in one joint, and spreads slowly. The spread of the disease is from the periphery to the centre. Usually the interphalangeal joints of the fingers are first affected, then the metacarpo-phalangeal joints, then the wrists, ankles, knees, and shoulders, and last of all the hip-joints. The temporo-maxillary and vertebral joints are usually affected sooner or later.

The joints are swollen with a fusiform appearance. There is marked limitation of movement, and in the late stages great deformity will be present. This deformity is due to the formation of adhesions around the joint, secondary contraction of muscles, and partial dislocation of the joint. In the hands the deformity takes the form of ulnar deviation of the fingers, and this is the most characteristic deformity of rheumatoid arthritis. The skin is atrophic and glossy. The muscles above and below the affected joints are very much wasted, but there is no alteration in tendon reflexes. Enlarged glands in the groin and axilla are not uncommon.

Of the constitutional symptoms, anæmia is most marked. This is of a secondary type. The pulse-rate is usually raised, the temperature rarely affected. The general nutrition is often impaired, and the patient is depressed. Mental symptoms are not infrequent in those cases that have been bedridden for many years, but it is probable that some factor other than rheumatoid arthritis is responsible for the insanity.

For some years, Forestier and others have advocated the use of gold salts in the treatment of rheumatoid arthritis. This is based on the view that rheumatoid arthritis is due to infection by tubercle bacilli of low virulence. Although this view has never been accepted in this country, we have seen remarkable improvement in many cases treated by this method. The mode of action of gold salts is not known. It may be that it acts by chemiotaxis, or it may be due to the action which the heavy metals in very small doses have on the bone-marrow and bones. The action of the heavy metals on bone and bone-marrow is similar to that of arsenic. If small doses are given to animals, the red marrow becomes hyperæmic, the fat cells disappear, and there is a decided increase in the number of leucoblastic cells. The erythroblasts are not increased. In the view of the writer, the favourable results obtained by gold salts are due to increased vascularity of the marrow.

Jacques Forestier, at a lecture given to the Ulster Medical Society (February, 1934), stressed the necessity for frequent observation of the blood sedimentation-rate. He held that if the blood sedimentation-rate was not raised, the arthritis was of a degenerative nature (osteo-arthritis), and gold salt therapy would not be successful. He held further that the sedimentation-rate is as important a guide to the treatment of rheumatoid arthritis as is the Wassermann reaction in syphilis. Our experience at the Mater Hospital has failed to confirm his views up to the present, but in view of the small number of cases at our disposal our findings cannot be considered conclusive. The blood sedimentation-rate has proved with us to be too variable a factor to be reliable. For example, one patient whose sedimentation-rate was 60 in one hour (Westgren's method) when suffering from a slight coryza, was 26 when taken one week later. Again, a case of gonorrhœal arthritis showed a sedimentation-rate of 120 for the first hour, but showed no improvement with gold salt therapy. Our present view is that the sedimentation-rate is not a reliable guide

in the selection of cases for treatment, and cases are now selected on clinical grounds alone.

If the toxic properties of the heavy metals be borne in mind, it will be obvious that patients who are suffering from disease of the liver or kidneys are unsuitable for this method of treatment. Gold is excreted by the kidneys, and if elimination is defective, accumulation of the drug is certain to occur. Some cases of severe toxic jaundice have been reported following gold therapy, and it is therefore important to exclude hepatic disease when possible.

Unfortunately, tests for liver function are far from satisfactory. The lævulose test is probably the best. The sedimentation-rate is lowered in functional disease of the liver, so that a sedimentation-rate of less than 6 would be a contra-indication to gold therapy.

The preparation of gold which we have used since January of this year is a substance known as myocrisin. This is an aqueous solution of aurothiomalate of sodium and is of very low toxicity. The initial dose is .01 gramme given intramuscularly. The injections are given at weekly intervals, and are increased gradually. At no time is the dose allowed to exceed .20 gramme. When two grammes have been given, the patient is allowed a rest of two months, and the course is repeated if necessary. The first two or three injections are definitely painful, but patients state that subsequent injections cause only very slight discomfort.

None of our cases has developed any toxic effects as a result of the treatment, but we have to keep in mind always that prolonged treatment, even with small doses, will cause eburnation of bone and degeneration of bone-marrow. Aplastic anæmia is a very real danger if excessive amounts of gold salts be used. The following toxic effects have been reported following the use of gold salts :—Cutaneous eruptions, lichen planus, jaundice, subcutaneous and submucous hæmorrhages, hæmatemesis, diarrhœa, hæmaturia, and anæmia. As our patients are treated at the extern department, each patient is required to bring a letter from her private practitioner to the effect that he is willing to co-operate with the hospital in the observation and treatment of the case. In the event of toxic signs arising, the patient would at once consult her doctor. The treatment suggested for such cases is the intravenous injection of .6 gramme of sodium thiosulphate in 10 c.c. of distilled water daily for ten days.

Fifteen cases have been treated by myocrisin since January, 1934. Fourteen were women, and their ages varied from 18 to 65 years.

The following case reports will give an idea of our experiences with gold salts therapy :—

Case 1.—Unmarried female, aged 24. Duration of illness, one and a half years. Fusiform swellings at proximal interphalangeal joints, with marked pain and limitation of movement. No ulnar deviation. Metacarpo-phalangeal and tarso-metatarsal joints also affected. Blood sedimentation-rate (Westgren's method) : First hour, 40; second hour, 65; twenty-fourth hour, 120. Treatment with myocrisin began on 18/1/34. Course of two grammes completed on 21/6/34. Improvement was extremely slow in this case, but at the end of the course there was no evidence of arthritis in the tarso-metatarsal or in the metacarpo-phalangeal joints. There was still slight swelling at the interphalangeal joints, but movements were free and

painless and the skin had lost the glossy appearance. She returned to work as a stitcher.

CASE 2.—Unmarried female, aged 38. Duration of illness, one year. Large fusiform swellings at proximal interphalangeal joints. No other joints affected. Blood sedimentation-rate 45 : 80 : 120. Treatment with myocrisin began on 8/3/34. This patient showed marked improvement after the second injection. The swellings decreased in a remarkable manner. After the sixth injection she insisted on returning to work, as her hands appeared to be normal. She had received .41 gramme of myocrisin. She is still at work, and visits hospital from time to time.

CASE 3.—Unmarried female, aged 20. Duration of illness, six months. Slight fusiform swellings on middle fingers only. Very little pain or limitation of movement. Blood sedimentation-rate 6 : 20 : 80. Treatment with myocrisin began 29/3/34. This patient ceased to attend after she had received a total of 1.21 grammes. The swellings had decreased a little in size, but as the condition had been very slight the improvement was not marked.

CASE 4.—Unmarried female, aged 19. Duration of illness, two years. Interphalangeal joints only affected. Slight fusiform swellings, and marked limitation of movement. Blood sedimentation-rate 14 : 35 : 110. Treatment began on 12/4/34. On 21/6/34, when this patient had received one gramme of myocrisin, the swelling and limitation of movement had entirely disappeared and she returned to work.

CASE 5.—Unmarried female, aged 20. Duration of illness, five years. Swellings at interphalangeal, metacarpo-phalangeal, carpo-metacarpal, wrist, and tarso-metatarsal joints. Marked swelling and deformity, pain, and limitation of movement. Blood sedimentation-rate 95 : 125 : 140. Treatment began on 26/4/34. This patient has now received 1.31 grammes of myocrisin, and is still under treatment. The improvement is very marked, although there is still some swelling at the carpo-metacarpal and wrist joints.

CASE 6.—Married female, aged 52. Duration of illness, four years. Slight swelling at interphalangeal joints, with marked limitation of movement. Blood sedimentation-rate 35 : 60 : 115. Treatment began on 21/4/34. This patient received .91 gramme of myocrisin, but there being no apparent benefit, she ceased to attend.

CASE 7.—Unmarried female, aged 61. Duration of illness, fourteen years. Very little swelling or deformity in hands. Marked creaking at left elbow joint. Pain and stiffness in neck. X-ray showed arthritis of intervertebral joints in cervical region. Blood sedimentation-rate 60 : 85 : 120. Treatment began on 29/3/34. This patient received 1.4 grammes of myocrisin. As there was no evidence of improvement, treatment was discontinued.

CASE 8.—Unmarried female, aged 65. Duration of illness, twelve years. Slight swelling in hands. Marked swelling at tarso-metatarsal and ankle joints. X-ray showed rheumatoid arthritis at ankle joints. Blood sedimentation-rate 45 : 82 : 126. Treatment began on 12/4/34. Received course of two grammes. This patient has made a very satisfactory improvement. She can now walk about two hundred yards with the aid of a stick. For the past three years she was unable to walk without assistance. The swelling had disappeared at the ankles, and the skin has lost its parchment-like appearance.

LONDONDERRY MEDICAL SOCIETY

THE fifth meeting of the session 1933-4 was held in the City and County Infirmary on 30th March, at 8.30 p.m. The president, Dr. W. Rankin, welcomed Mr. S. T. Irwin, who was the lecturer for the meeting. There was a very large attendance of members. Mr. Irwin chose as his subject, "The Treatment of Gastric and Duodenal Ulceration." It would be very difficult to give an adequate epitome of this address, as it itself was really a very condensed epitome of a vast amount of material. Suffice to say that it was listened to with the closest attention by all present. Perhaps the most pressing point enunciated was the very great importance of trying to diagnose a pre-ulcer stage, and as a corollary the importance of medical treatment in young subjects with an ulcer of short duration. If this stage is not treated adequately and efficiently, the complications such as obstruction, bleeding, etc., all too frequently occur, and as the years advance the efficiency of medical treatment becomes less and less. The feeling of the members present was all in favour of this point of view so clearly and succinctly put forth by Mr. Irwin.

At the sixth meeting of the Society, the president and members had the pleasure of welcoming Dr. W. W. D. Thomson, Professor of Medicine of Queen's University, Belfast. Dr. Thomson lectured on "Hyperpiesia." The main theme of his address was that the disease is not so black as it is painted—a motif that was very much to the liking of everybody who listened to him. He pointed out that, with reasonable care and attention to good common-sense hygienic rules, a patient afflicted with a high blood-pressure stood a reasonably good chance. One of the chief causes of patients doing badly was mental worry, and far too frequently the chief worry was blood-pressure phobia, and it may be added that this is in no small measure due to the activities of the lay press.

A very important part of Dr. Thomson's address lay in the question of differential diagnosis between renal disease and hyperpiesia, the main point being in the assay of the diuresis brought about in the two diseases by the drinking of a given amount of water under certain specified conditions.

On the 9th June a most enjoyable golf match was arranged at Portrush, between members of the Ulster Medical Society and members of the Londonderry Medical Society. It is perhaps just as well that this is not a sporting journal, and it will not be necessary to give details of the individual matches, because nobody seemed to worry very much who won, which is precisely what made this such an enjoyable fixture. On the motion of Professor R. T. Johnstone, seconded by Dr. John Watson, it was decided to hold a similar meeting, if possible, on the second Saturday of June annually.

On Thursday, the 14th June, on the invitation of Dr. and Mrs. John Watson, the Society held an informal garden party in the Gransha Asylum grounds. This was unfortunately marred by bad weather, but there was an exceedingly good turn-out, and everybody made the best of it.

J. A. L. JOHNSTONE, *Hon. Secretary.*

19 Clarendon Street, Londonderry.

ULSTER MEDICAL SOCIETY

THE Council begs to present the seventy-second annual report of the Society.

The roll of the Society now stands as follows :—

	This Year	*Last Year*
Honorary Fellows - - -	7	9
Life Fellows - - -	13	11
Life Members (under old regulations)	2	2
Fellows - - -	274	243
Members - - -	53	59

During the session the Society has lost by death :—Sir William Whitla, M.A., M.D., LL.D., Honorary Fellow, President 1886-7, 1901-2; Sir George H. Makins, G.C.M.G., C.B., F.R.C.S.Eng., Honorary Fellow; Professor Andrew Fullerton, C.B., C.M.G., M.D., M.Ch., F.R.C.S.I., F.A.C.S., Honorary Fellow, President 1919-20; Dr. J. H. Gillespie, Fellow since 1930.

Ten meetings have been held during the session, and the attendance has been very satisfactory.

Among the speakers were Dr. J. P. Martin of the National Hospital for Nervous Diseases, Dr. Jacques Forestier of Aix les Bains, Dr. Scott Pinchin, and Dr. Morlock.

The laboratory meeting provided many exceptionally interesting specimens.

The annual dinner was again held in the Medical Institute, and although the numbers were not so large as they had been the previous two years, it was a very successful function.

The Hanna Golf Cup was won by Mr. Hardy Greer, the competition being played off at the course of the Royal County Down Club.

During the session a new epidiascope was purchased, and is giving satisfactory results.

J. A. SMYTH, *Honorary Secretary.*

PROFESSOR JOHN A. MILROY, M.A., M.D.

19th September, 1934

THE medical school of Queen's University has suffered a heavy loss in the death of Professor John A. Milroy. A man of great learning, of whom the University was proud, his place will sadly be missed, not only as a member of the academic staff, but as a man. No member of Queen's ever gained the affection of his students to a greater degree; and nowhere will his loss be mourned in greater measure than amongst those students who have passed through his classes. Honest in outlook, he could see no guile in others, and his sterling character and gentle manners influenced for good all those who came his way. His life was not in vain, and his memory will ever be fresh wherever a Queensman lives.

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POST-GRADUATE COURSE FOR NATIONAL HEALTH INSURANCE PRACTITIONERS

At the request of the Ministry of Labour (N.I.), a post-graduate course in medicine and surgery for National Health Insurance Practitioners was held in conjunction with the clinical staffs of the Royal Victoria and Mater Infirmorum Hospitals, Belfast, and with the pre-clinical Medical School of Queen's University, in September, 1933. So successful was this course that the Ministry of Labour (N.I.) again requested the organization of a similar course in 1934. This course was arranged for the second fortnight in September, and some forty-eight practitioners attended.

The morning sessions of the course were devoted to the clinical examination of patients, and to discussions on the diagnosis of the different cases and on the course of treatment to be followed. The afternoon sessions consisted of lectures and demonstrations on pathology, bacteriology, and biochemistry as applied to the diagnosis and treatment of diseases, and to discussions on public health problems, particularly those affecting rural communities. It also included two valuable discussions, led by Dr. James Boyd, the Ministry's Chief Medical Officer, on the working of the National Health Insurance Act as applied to Northern Ireland.

Attendance on such a course is of very great value to the busy practitioner, and focuses his attention on the relative values of the more useful of the newer methods of diagnosis and treatment. It enables him to see and study at first hand the practice and results of these methods, and thus help to keep the standard of his practice up to date, so that he can be of the greatest possible assistance to the community in the control of disease and in guarding the health of the people under his charge.

Before the formal lectures and demonstrations began, Professor R. M. Henry, Acting Vice-Chancellor, Queen's University, Belfast, delivered an inaugural address to the members of the class, in the Institute of Pathology of Queen's University. This address was very cordially received and much appreciated by the members present. Professor Henry began by extending a welcome to all the members of the class to the Medical School of Queen's, and then dwelt briefly on the importance and advantages of post-graduate refresher courses such as that on which they were about to take part in the University, the Royal Victoria and the Mater Infirmorum Hospitals. He trusted that the time thus spent by them would be profitable not only to them as medical practitioners, but to the many patients who had entrusted their lives to them.

The organization of the programme and the general arrangements for the course were in the hands of Dr. R. H. Hunter, who acted as guide and cicerone to the members during the whole period which it lasted.