Researches on rheumatism / by F.J. Poynton and Alexander Paine.

157 nur

RESEARCHES ON RHEUMATISM

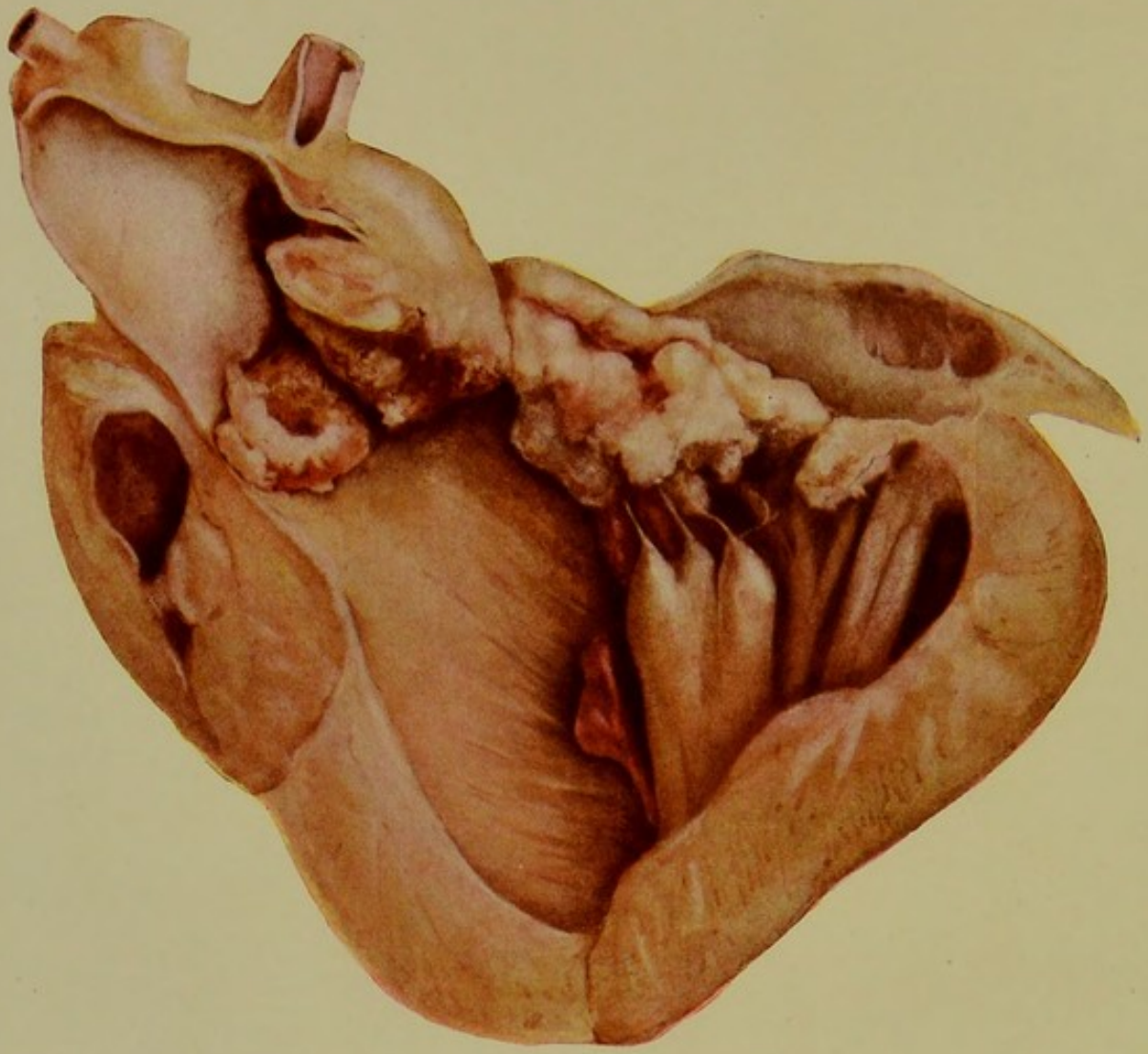


FIG. A

To illustrate Paper No. XXIII upon mitral and aortic disease of rheumatic origin (p. 318).

FIG. A. The heart of a rabbit showing endocarditis of the mitral and aortic valves. The heart has been greatly enlarged for the more convenient comparison with the human heart. The vegetations on the mitral valve are very extensive and are in continuity with equally extensive ones upon the aortic cusps.

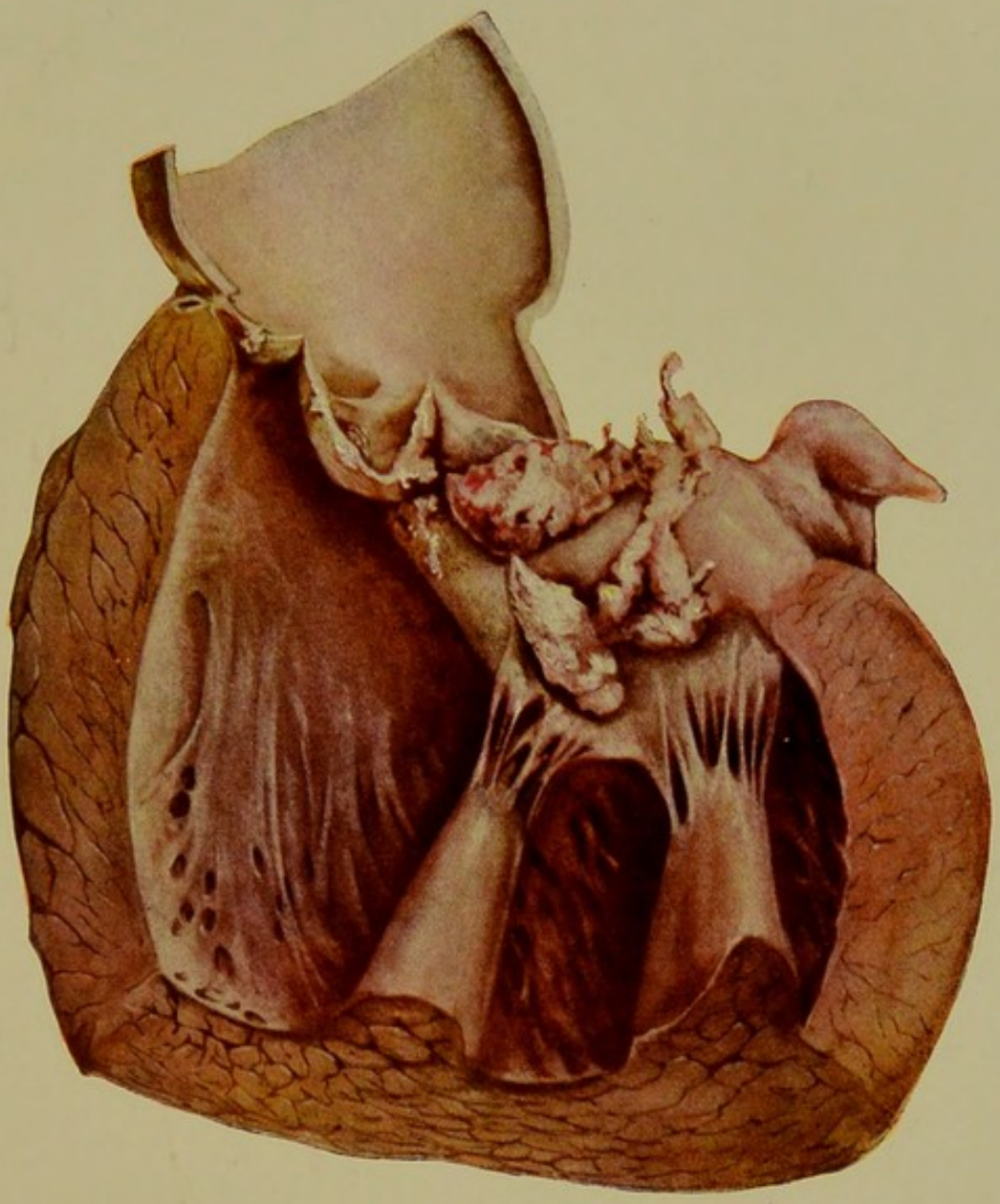


FIG. B

To illustrate Paper No. XXIII upon mitral and aortic disease of rheumatic origin (p. 318)

FIG. B. A human heart showing aortic and mitral endocarditis. The vegetations on the aortic flap of the mitral are in continuity with extensive vegetations on the contingent aortic cusp. The other cusps are affected in lesser degree. The mitral valve is not opened.

[From *Quarterly Journal of Medicine.*

RESEARCHES ON RHEUMATISM

BY

F. J. POYNTON
M.D.LOND.
Fellow of the Royal College of Physicians of London, Vice-Dean of University College Hospital Medical School, Senior Physician to Out-patients at University College Hospital, London, and at the Hospital for Sick Children, Great Ormond Street, Physician in Charge of the Children's Ward University College Hospital

AND

ALEXANDER PAINE
M.D. (State Medicine) Lond., D.P.H.Eng.
Director of the Cancer Hospital Research Institute London

WITH FRONTISPIECE IN COLOUR AND 106 ILLUSTRATIONS

LONDON
J. & A. CHURCHILL
7 GREAT MARLBOROUGH STREET
1913

BALLANTYNE & COMPANY LTD
TAVISTOCK STREET COVENT GARDEN
LONDON

TO

DAVID BRIDGE LEES

M.A., M.D.Cantab., M.D.Durham, F.R.C.P.Lond.
Consulting Physician to St. Mary's Hospital, London, and to the
Hospital for Sick Children, Great Ormond Street.

IN GRATEFUL REMEMBRANCE OF HIS UNFAILING ENCOURAGEMENT, IN RESPECT FOR HIS EMINENCE IN THE MEDICAL PROFESSION AND IN ESTEEM FOR HIS QUALITIES AS FRIEND AND TEACHER THIS BOOK IS DEDICATED BY HIS FORMER PUPILS

F. J. POYNTON
and
ALEXANDER PAINE

PREFACE

We have collected in this volume the chief papers bearing upon a research on the subject of rheumatism which has extended over a period of fifteen years. In so doing we are well aware that few have the time to spend over reading the details of such investigations, but should the essentials of this research be eventually established, we feel that this book will stand as a landmark in the history of rheumatism in this country. Some of these papers were written before we demonstrated what we believe to be the exciting cause of the disease ; others elucidate the nature and action of that cause ; others, again, extending the main thesis, deal with allied conditions. At the conclusion of the volume the bearing of these investigations upon clinical medicine and public health is considered in a special article. Owing to unavoidable circumstances we have from time to time been unable to collaborate, but others have then come to our assistance. Dr. Vernon Shaw, who had shown the identity of the diplococcus we isolated with that described by Professor Wassermann and Drs. Ainley Walker and Beaton, and who had proved the susceptibility of monkeys to the infection, assisted us in a paper on multiple infections. Dr. Gordon Holmes brought his deep knowledge of the pathology of the nervous system to our aid in another upon chorea. Dr. G. F. Still took part in the early paper upon the rheumatic nodule, and Dr. D. B. Lees inspired and collaborated in the first paper upon acute dilatation of the heart. Such a prolonged investigation as this would have been impossible without the help of many friends not only at St. Mary's and University College Hospitals and the Hospital for Sick Children, Great Ormond Street, but also at other institutions. Should this work live—and many of the recorded facts can never be swept away whatever the ultimate fate of their interpretations—we can truly write that it has been a result of English medicine, which opportunity has called upon us to bring to a focus. We

recall with pleasure and gratitude the early days when Mr. H. G. Plimmer aided us in acquiring the necessary methods for such an undertaking.

The illustrations have been chosen with the intention of demonstrating the intimate processes of rheumatism in the body, and for the purpose of acting as a pictorial guide to our main conclusions. The kindness of Messrs. Bale, Son and Daniellsson, Messrs. Adlard and Son, the Clarendon Press, the *Lancet*, and *Medical Press and Circular* has enabled us to obtain many of the illustrations we thought desirable. All of them are original, and some have never been reproduced before. Our best thanks are due to our artists, Messrs. Ford and Shiells, who have assisted us during the last thirteen years. We must also thank the various societies, journals, and publishers for permission to reprint our papers, due acknowledgment for which is given with each of them.

To Messrs. J. and A. Churchill we are indebted for carrying out the publication of this book in a manner which has given us much satisfaction and for the greatest courtesy and assistance.

In conclusion, with no intention of appearing to be presumptuous, we would venture to emphasise the value in medical research of the combination of the clinician and bacteriologist working side by side, for the clinician serves to keep the bacteriologist sane and the bacteriologist to keep the clinician honest.

CONTENTS

INTRODUCTION

We ask the reader to look upon this collection of papers as a contribution to the study of Rheumatism, which is the result of an investigation extending over a very interesting period in the history of the disease.

When we approached the problem of the ætiology there had been a growing conviction among many experienced clinicians that the acute rheumatism of childhood was the result of an infective process, but the evidence other than clinical, was, in this country, meagre in the extreme. Dr. Mantle in 1886 had made some interesting observations upon the bacteriology, and Popoff in Russia had in 1887 produced some remarkable experimental lesions with a diplococcus. In France, Triboulet and Apert had also studied a diplococcus, and in Germany Westphal, Wassermann and Malkoff had anticipated some of our own results while our investigations were in the course of development. It may, however, be stated that in this country no pathologist had produced with any micro-organism isolated from the lesions of acute rheumatism such results as endocarditis, myocarditis, or pericarditis, and not even multiple arthritis was recognised as a result of experimental infection from rheumatic lesions.

It is difficult to realise how the production of these experimental results, not once, but repeatedly has influenced English writings and altered almost unconsciously the views that were held upon rheumatic processes. Yet who now would believe that the structure of a vegetation in rheumatic endocarditis was produced by uric acid circulating in the blood

or by a disturbance of some nervous process in the brain, or as a result of a surfeit of meat or carbohydrate foods? The rheumatic nodule so well recognised as a very characteristic lesion in childhood lost its mystery when it was discovered that it can be experimentally produced by intravenous inoculation of a micrococcus and was in itself a complete rheumatic lesion upon a small scale. Chorea, one of the most remarkable of all the clinical phenomena, becomes at least more comprehensible when we find that in the same patient a micrococcus isolated from an acute rheumatic pericarditis may also be discovered in the pia mater and brain, and further that, when inoculated intravenously into animals, it may also be found in these situations producing irregular involuntary movements by virtue of the tissue changes that result. It is a step forward and surely one of far reaching practical importance that we can now state with confidence that a micrococcus gaining access to the system from an inflamed tonsil may produce heart disease with or without the involvement of other systems. Every medical man in this country acquainted with the ravages of rheumatic heart disease will, we think, recognise that in the establishment of such a fact as this and with the proof of the infective origin of rheumatic carditis there is brought into existence a new hope for the victims of heart disease. No marvellous cure indeed declares itself, but great possibilities arise for the best of all treatment, that of prevention. Those who are deeply interested in such important results as these may like to study some of the details of the investigations that led to these conclusions.

Students of arthritis will recognise that, in the production by intravenous inoculation of non-suppurative lesions of joints varying both in intensity and duration, the great field of that which for want of a better term we may call rheumatoid arthritis is opened out. It is a curious result, seeing that we first demonstrated non-suppurative arthritis as an outcome of experimentation with a micrococcus obtained from

obvious rheumatic lesions, that often enough at the present time the term "infective arthritis" is used to express a condition which is to be differentiated from acute rheumatic arthritis. Time alone will rectify this perversion of our interpretation and we feel that we must be content with the belief that these fundamental experiments have cleared away some of the mysteries surrounding "rheumatoid arthritis." Three observations in the problem of arthritis are of particular importance, one is that the same infective agent may produce all varieties of non-suppurative arthritis from a simple synovitis to an osteo-arthritis ; another that the acute and very chronic lesions produced by experiment may be associated with effusions which are sterile, and the third that an intravenous infection may produce a monarticular arthritis.

Another aspect of the subject of acute rheumatism worthy of attention and brought into prominence by these papers is the variety of lesions produced by the infection. Undoubtedly it resembles its allies in possessing a proclivity for attacking certain of the tissues, but from the nature of its pathology there is no theoretical barrier to the possibility of its attacking any tissue or system in the body. We are accordingly justified in studying the disease upon the broadest lines, and with minds alert to the possibility that there are in man rheumatic affections which are as yet hardly accepted as of that nature, for example a broncho-pneumonia, a nephritis, a peritonitis or an appendicitis. Again it is important to remember that, if this infection is of the nature we believe it to be, it will probably show in the tissues all grades of virulence. To us it has long seemed clear that the nature of the rheumatic processes has been judged too rigidly by the criterion of the acute arthritis. This particular phase of the infection, frequent enough we admit, has been looked upon as representing the life history of the disease and this view has been encouraged by the relief given to this particular phase by the salicylate treatment. With this view however,

we are not in accord and believe that on insufficient grounds cases of stubborn non-suppurative arthritis have been declared to be non-rheumatic in nature.

This question becomes one of far greater importance when endocardial lesions are considered, and to us it has seemed to be unlikely that a rheumatic endocarditis need be necessarily a benign or healing lesion. To this important point we have devoted some of the most elaborate of our papers.

The problems in the bacteriology of rheumatism are both difficult and fascinating and it is only due to ourselves to point out that new facts have necessarily been forthcoming in this comparatively young science during the fifteen years covered by these investigations. Accordingly the bacteriologist of to-day will not expect to find in a paper written in 1900 the details that are demanded now. It may be said that bacteriology in this country was only in its very infancy at the time that we were students and that then necessarily much importance was attached to certain standards which the natural development of the science have shown to be too arbitrary. Certain staining methods and certain morphological details for example became looked upon as tests of the specificity of various micro-organisms and sometimes on insufficient grounds the specific micro-organism and the specific disease were looked upon as almost identical in the sense that the disease was thought to be entirely dependent upon the infective agent. The possibility of the evolution of micro-organisms was in danger of being overlooked. There can be no doubt that circumstances may arise in which the virulence of a micro-organism may become so extreme and so special that it may overcome the most healthy and destroy them by a disease which runs a peculiar course, but it is also clear that in many instances a micro-organism, though to tests *in vitro* and in its morphology apparently unaltered, may lose entirely its specific powers and revert to a saprophytic state. Again it is recognised that the specific virulence may greatly depend

upon the condition of the host at the time of infection. Thus a specific infective disease may be by no means entirely dependent upon the particular infective agent, for it may also need some special conditions in the patient. Because a micro-organism may have the same morphology and share in common certain properties *in vitro* with one believed to be specific it does not necessarily follow that it is identical in its essential property, namely the ability to produce a particular disease.

These difficulties are perhaps at their greatest in the streptococcal group, but when our first papers were brought forward this group was but partially recognised and to many the term "streptococcus" suggested *the* streptococcus pyogenes. The complexity of this group is now thoroughly appreciated, but thirteen years ago any investigation in which a streptococcus was claimed as the cause of a disease was in the greatest danger of being brushed aside with the comment that the authors had rediscovered the streptococcus pyogenes. Recognising the possible fallacies contained in the term "specific" micro-organism, we declined to go further than to claim that the diplococcus we had isolated was the only cause we could find of a specific disease. We relied and still rely on the belief that the nearest approach that can be reached in the establishment of the causal agency of any micro-organism to a disease is the isolation of it from the acute lesions in man and the reproduction of these with it in animals. It is not a perfect test and from the standpoint of clinical medicine in some respects unsatisfactory. But the results obtained in living animals under these circumstances bring us we believe nearer the truth than do any tests of a micrococcus outside the living body conducted in the laboratory.

Such an attitude as this, however, demands of us that we bring good evidence that the disease we claim to be specific is indeed a peculiar one. Our investigations, both clinical and pathological, on this have been extensive and searching

and they are fortunate in receiving, we believe, almost the unanimous support in this country of those who are thoroughly acquainted with rheumatism studied from its purest source, its occurrence in childhood. Among the many criticisms that have been made upon the investigations, the definite objection that acute rheumatism is not a peculiar disease we have been prepared to meet with determination and conviction by the statement that it is one of the most special and definite diseases in this country, although it is quite possible that there may be different types which the future will determine just as there are different types of pneumococcic infection. In these papers we have devoted much attention to these problems which are clearly of cardinal importance.

There is another important result of our attitude towards this question and one to which we are anxious to draw the reader's particular attention for it limits very definitely the scope of our research. We have never claimed that the diplococcus was so specific in its cultural and laboratory tests that obtaining a micrococcus morphologically similar from a lesion of unknown origin, we could say that the lesion was rheumatic. We have only claimed that when a diplococcus with such characters as we have described is obtained from a lesion of undoubtedly rheumatic origin and produces the experimental lesions of this disease, that it is the causal agent. With the utmost caution and with an experience of the micrococcus founded upon some years of study we have isolated it from the diseased tonsils of the rheumatic, and believe that we have proved that this micrococcus was identical with that isolated from acute rheumatic lesions. But we are well aware of the extreme difficulty of this step and the results we arrived at were considered with this difficulty fully before us. We would point out that we have never relied upon the production of arthritis in rabbits as a proof of rheumatism, as any who read our first paper upon the ætiology

will at once recognise. There is no doubt that this limitation in the research is a very important one and impairs the practical application of its results, but we have not been primarily concerned with finding a "cure" for acute rheumatism, but rather with the elucidation of the nature of the disease and the bearing that this may have on the prevention of much heart disease, chorea and arthritis. The difficulties presented by the streptococcal group of micrococci are extreme, and such points as we established regarding the rapid loss of virulence but remarkable resistance in the saprophytic stage, the size, the staining reactions and acid producing properties of the diplococcus are recorded in these papers and have met with confirmation from others.

We have answered to the best of our ability the numerous criticisms that we have encountered. One criticism however it is impossible to answer and that is the negative results that have been obtained by many bacteriologists. Such a question of fact can only be met by pointing to the corroboration of our results by others.

We have altered but little in the original papers and such alterations as have been made are chiefly concerned with the prevention of wearisome reiteration. The experimental studies are given in detail, but they are in such a form that those who wish to omit them can easily do so. A few alterations have been made in the chronological order but these are of slight importance. We have linked the papers together by prefaces which indicate the line of thought and the new facts that each contains. The various contributions are grouped into three parts. The first contains those papers which were written before the demonstration of the ætiology and which were steps antecedent to this. The second, a large group, contains those which demonstrate the ætiology and enquire into the nature of the rheumatic lesions, both human and experimental. This group is subdivided into a group dealing with the cardina steps in the demonstration of the ætiology and others dealing

with arthritis, chorea and other nervous manifestations, and with heart disease. Among these papers also are some which touch upon such debated problems as the cause of osteo-arthritis, the nature of multiple infections, and appendicitis. The last group contains the practical applications of the investigation to clinical medicine and public health. We have included the first group because two of the papers are of some historical interest. The joint one with Dr. D. B. Lees on acute dilatation of the heart helped to place on a firm basis the outstanding importance of the myocardium in rheumatic heart disease. The pathological investigation on the myocardium demonstrated the occurrence of those focal lesions which have later attracted so much attention under the name of "submiliary nodules" in connection with the specific cell of the rheumatic lesions and the mechanism of cardiac arrhythmias. These papers also favoured the view that the rheumatic processes were the results of an infection. Lastly reference to them will show that our teachers and we ourselves recognised the important part taken by the myocardium in heart disease, which the introduction of new methods has of late so strongly emphasised.

The difficulties in the investigation of rheumatism as we have met with them are considerable, and it may be of some service to others if we mention some of those which have chiefly impressed us. Although the acute disease in childhood is rife in this country, fatal cases are not very frequent and this necessarily makes progress slow. Then as we discovered by experience the micrococcus is rapidly destroyed by the living tissues and the favoured sites are not as in tuberculosis those which are in communication with the exterior but are closed cavities such as the pericardial, synovial, and cranial. The infection is moulded on the pyæmic type, that is it produces essentially local lesions, and this combined with the great resistance of the tissues makes it difficult to isolate the micrococcus from the exudations even if their presence

be obvious in films. Then, again, it is a delicate micrococcus, and living in the local lesions its isolation from the blood is not to be as a rule expected, and the maintenance of the virulence we have found difficult and have repeatedly directed attention to the failure of peptone-agar and peptone-bouillon as satisfactory media. The demonstration of the micro-organism in the tissues is not easy for the reason given above and because it is minute and not tenacious of Gram's stain. Over this point we had many difficulties until experimental investigation came to our assistance. In our papers we have repeatedly dwelt upon these difficulties which we have only succeeded in overcoming by the closest attention to all details.

There was another initial difficulty not perhaps at first so apparent, the necessity for obtaining some firm basis from which to start. It is clear that the first step must be to obtain some position or some guide which can be made reasonably safe and to which we can fall back for support and assistance. The acute rheumatism of childhood was the basis for this investigation, because it is frequent in its occurrence and also not uncommonly fatal, and thus clinical, pathological and histological facts can be obtained. The greater part of this book is concerned with the details of this disease, and because it is our basis we have opposed with the utmost determination any attempts to make us draw back from our contention that it is a specific disease. If this point is yielded we drop back once more into the chaos of those disorders covered by the all-embracing term " rheumatism " and much time will be lost then in disputing as to what is to be looked upon as rheumatic.

Those who have not paid especial attention to rheumatic affections may think that we have fallen into the trap of believing that everything we met with showing the least resemblance to acute rheumatism was in reality of that nature. Such however is not the case: we certainly have ventured from time to time from our basis to explore allied disorde

by the light of ascertained facts but we have always remembered that these ventures were tentative. The establishment of the cause of a most important disease among those classed in general terms as "rheumatic" is, we believe, the first and essential step in the study of the problem and then by comparatively easy stages the remainder of the group will be eventually elucidated. It is not difficult to see how the horizon widens as an outcome even of the results recorded here. If there is a definite infective agent for some form of "rheumatism" that agent must differ in virulence and resistance in different cases, and in these possibilities lies a large field for observation. The morbid anatomy resulting from the toxines of this infection will serve as a basis for comparison in the study of the allied disorders. Again, the results of multiple infections can be more easily interpreted when the results of the simple infection are understood.

This investigation we realise only touches upon the greater problem of "rheumatism." We have not thrown light upon the actual nature of the toxines, and many of the questions as to the more chronic forms of arthritis have yet to be explained. The field is a very wide one and of the greatest interest and importance in this country in which rheumatism is so frequent.

PART I

PAPERS PUBLISHED BETWEEN 1898 AND 1900, PREVIOUS TO THE DEMONSTRATION OF THE DIPLOCOCCUS, WHICH WE LOOK UPON AS THE BACTERIAL CAUSE OF ACUTE RHEUMATISM

PAPER NO. I

ACUTE DILATATION OF THE HEART IN THE RHEUMATISM AND CHOREA OF CHILDHOOD.

By D. B. LEES, M.D. and F. J. POYNTON, M.D.

(From vol. lxxxi of the *Medico-Chirurgical Transactions*.)

This paper upon dilatation of the heart, inspired and collaborated in by Dr. D. B. Lees, gave us one of the chief clues as to the line of subsequent investigation. For the demonstration of the clinical importance of this dilatation in rheumatism suggested a resemblance between the behaviour of the heart in this disease and in others of undoubtedly infective origin. Further, the view was favoured that a minute study of the myocardium in rheumatism would discover lesions, which in their turn would support the theory that the process was of an infective nature.

The paper itself was a sequel to one by Dr. D. B. Lees upon acute dilatation of the heart in rheumatic fever read the same evening. The methods of investigation that were employed in both of them were identical, and their intention was to establish on a clinical basis the reality of acute dilatation in the carditis of rheumatism, and also to direct attention to the comparatively minor importance of pericardial effusion as an explanation of the great increase in the area of precordial dullness that may occur in severe carditis.

The extensive analysis of fatal cardiac rheumatism in Appendix C is a useful reference Table for the study of the various lesions that may occur.

This paper embodies the results of a joint investigation of the subject of acute dilatation of the heart in rheumatism and chorea made at the Hospital for Sick Children, and it also includes an account of certain enquiries in further elucidation of the subject. These enquiries comprise:

1. Observation on the size, strength, and sounds of the heart in healthy children.

2. Observations on the condition of the heart in rheumatic and choreic children under the care of physicians other than Dr. Lees. We tender our thanks to Dr. Cheadle, Dr. Barlow, Dr. Phillips, and Dr. Penrose, for kind permission to make use of their cases.

3. An analysis of 150 fatal cases of rheumatic heart disease in children under twelve years of age, taken from the records of the Hospital for Sick Children and from those of St. Mary's Hospital.

Before proceeding to discuss the condition of the heart in rheumatic and choreic children we wish, in order to obtain a standard of comparison, to draw attention to observations on the size, strength, and sounds of the heart in children free from rheumatism. These were carried out partly in the surgical wards of the Hospital for Sick Children, in forty-five cases under the care of Mr. Owen, Mr. Morgan, and Mr. Pitts, who kindly allowed us to use their patients; and partly at Marlborough College, where the hearts of thirty-five healthy boys of twelve and thirteen years were examined by the permission and with the kind assistance of Dr. Penny, medical officer to the College, to whom also we offer our thanks.

All these observations were made with the child in the same posture—on the back, with the left arm abducted. The results are given in detail in Appendices A and B. We may briefly summarise them as follows:

In children aged from seven to twelve years the area of cardiac dullness (by which we mean the nearest approach to the actual size of the heart that can be obtained by percussion) extends upward to the third costal cartilage on the left side, thence downward and to the left to the fourth space just internal to the nipple, or even as far as the nipple-line. Crossing the middle line above, it extends in the fourth right space three quarters of an inch to the right of the median line, a bare fingerbreadth to the right of the sternal margin. As it passes downward it tends slightly inward before it reaches the hepatic dullness, and then recrosses the middle line to reach the apex.

In children under seven years of age the cardiac dullness extends as far as the left nipple-line more frequently than is the case in older children.

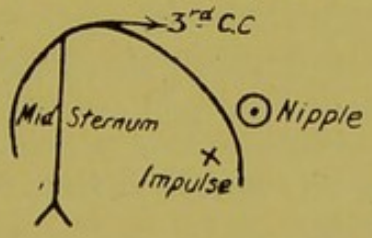
In the boys between twelve and fourteen, the left limit of the cardiac dullness was almost invariably distinctly internal to the left nipple-line, on the average about three quarters of an inch from it, and reached the fifth left rib or more frequently the fifth space.

In healthy children the cardiac impulse is usually internal to the left limit of the dullness, often markedly so. The action of the heart is regular. At the apex, the first sound is longer than the second. At the base, the second sound is louder on the left side than on the right, though both have a distinct relative sharpness. Soft blowing systolic murmurs are sometimes heard, most frequently in the fourth space internal to the impulse, sometimes at the base, more rarely at the apex; they may be modified by position. When these murmurs occur, the area of the heart is often rather larger than normal the general physique more feeble, and the child anæmic.

So far as regards the position of the cardiac impulse and its relation to the nipple, in younger and in older children, our results are in accord with those of Stärck and of Dr. Archibald Garrod quoted by the late Dr. Sturgess in the Lumleian lectures in 1894. But in determining the "cardiac dullness" we have rejected the "superficial dullness" and endeavoured to ascertain the true outline of the heart.

We conclude this section of our paper by showing with the lantern the area of cardiac dullness in a healthy boy of

Healthy boy, aged 12.



twelve, to serve as a standard of comparison for the tracings taken from rheumatic and choreic children.

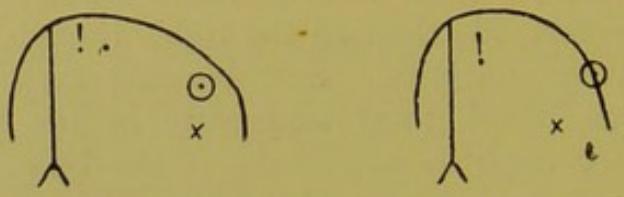
We now proceed to show tracings taken from the hearts of children suffering from rheumatism or from chorea, and would premise that *the several tracings in each case were always taken without reference to previous tracings from the same case.*

The varying severity of the cardiac affection makes it desirable to arrange our observations in four groups.

GROUP I. *First attacks of mild subacute rheumatism, in which there was no pericarditis, and either no murmur or only a systolic murmur best heard internal to the nipple.*

CASE 1. E. S—, aged 12, admitted into St. Mary's Hospital under Dr. Cheadle October 9, 1897, for moderate articular rheumatism.

E. S—, aged 12. Rheumatic fever, first attack.



No. 1. Oct. 10, 1897. No. 2. Oct. 26, 1897.

! accentuated pulmonary second sound. * systolic murmur. × impulse.

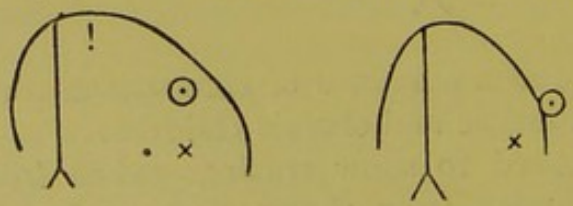
October 10. First tracing. Temperature normal. Impulse in the V.N.L. Area as shown. Short first sound. Accentuated pulmonary second.

16*th*. A slight rise of temperature (to 99.8°), and a soft systolic murmur heard internal to the impulse.

26*th*. Second tracing. Steady recovery had taken place. Temperature normal. Impulse internal to V.N.L. Area as shown. Systolic murmur very faint. It disappeared two days afterwards.

CASE 2. F. D—, aged 11, admitted into St. Mary's under Dr. Lees, April 6, 1897, with mild articular rheumatism.

F. D—, aged 11. Rheumatic fever, first attack.



No. 1. April 7, 1897. No. 2. April 17, 1897.

! accentuated pulmonary second sound. * systolic murmur. × impulse.

April 7th. First tracing. Temperature 102°. Impulse diffuse. Area as shown. Soft systolic murmur internal to impulse. Loud pulmonary second.

8th. Temperature fell to normal.

17th. The boy well. Second tracing. Impulse more definite, and internal to the nipple. Area diminished. No murmur.

CASE 3. E. D—, aged 9, admitted into the Hospital for Sick Children under Dr. Lees, February 29, 1896, for articular rheumatism.

E. D—, aged 9. Rheumatic fever, first attack.

No. 1. March 1, 1896. No. 2. March 5, 1896. No. 3. April 7, 1896.

! accentuated pulmonary second sound. * systolic murmur. × × diffuse impulse.

March 1. First tracing. Temperature 101.2°. Impulse diffused, and external to V.N.L. Faint systolic murmur internal to the impulse. Loud pulmonary second.

5th. Second tracing. Increase in cardiac area. Salicylates were now pushed, and the dilatation slowly subsided.

April 7. Third tracing. Impulse definite and internal to V.N.L. Area diminished. Systolic murmur gone.

GROUP II. *First attacks of chorea without history of previous rheumatism.*

The occasional occurrence of dilatation of the heart in chorea has been noted both by Dr. Garrod and by Dr. Osler. We find that it is common, even in cases in which there is no indication of rheumatism other than the chorea and no history of any previous rheumatic attack. In thirty-three cases without history of previous rheumatism, and in many of them without evidence of present rheumatism, we found that the area of cardiac dullness extended to the left of the nipple-line (usually about one finger-breadth) in no fewer than twenty-

nine, and in sixteen of these the impulse also was external to the nipple. On the other hand, in only three of them was there evidence of increase of the cardiac dullness towards the right. The auscultatory signs were noted in twenty-eight cases; in twenty-four of these the first sound was short, or accompanied by a faint systolic murmur. Tracings were taken in all the thirty-three cases, but a day was always allowed to elapse after the child's admission into hospital before the first determination of the cardiac outline was made. We now show two examples illustrating the condition of the heart in typical cases.

CASE 4. W. A—, aged 12, admitted into St. Mary's Hospital, October 19, 1897, under Dr. Lees, for chorea of moderate severity.

W. A., aged 12. Chorea, first attack.

No. 1. Oct. 20, 1897. | No. 2. Nov. 19, 1897. | No. 3. Jan. 3, 1898.

! accentuated pulmonary second sound. * systolic murmur. × impulse.

October 20. First tracing. Temperature 100.2°. Heart's action irregular. Impulse external to nipple. Area as shown. First sound remarkably short. Systolic murmur over pulmonary artery; loud pulmonary second.

During the early part of November there was some irregular pyrexia, and a rheumatic erythema appeared.

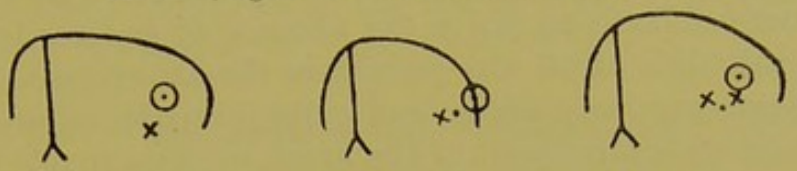
November 19. Second tracing. The area had increased, and a soft blowing murmur could be heard internal to the nipple. After this there was gradual and slow recovery.

January 3, 1898. Third tracing. Area diminished. Chorea and murmur gone.

CASE 5. M. M—, aged 10, admitted into the Hospital for

Sick Children, March 17, 1896, under Dr. Penrose. Chorea distinct, and of five weeks 'duration.

M. M—, aged 10. Chorea, first attack.



No. 1.
March 18, 1896.
× × diffuse impulse.

No. 2.
April 4, 1896.
× impulse.

No. 3.
April 9, 1896.
. systolic murmur.

March 18. First tracing. Temperature 99°. Impulse just internal to V.N.L. Area as shown. Basic systolic pulmonary murmur ; accentuated second sound.

April 4. Second tracing. Chorea nearly well. Area of dullness much diminished.

9th. Third tracing. The child had been getting up, but on the 8th had a little pyrexia, and a relapse of chorea. She was sent back to bed. This tracing shows an increase in the area.

She subsequently entirely recovered.

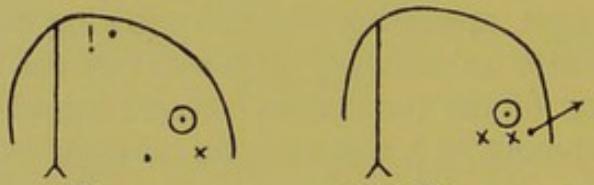
It is clear, therefore, that in first attacks of rheumatism and in first attacks of chorea there is often a definite increase in the cardiac area, appearing and disappearing under observation ; there is also an outward movement of the impulse, and an accentuation of the pulmonary second sound ; sometimes there is development of a soft systolic murmur internal to the nipple ; occasionally there is irregularity. Evidence of active rheumatism may be present also ; such as arthritis, or erythema or there may be pyrexia alone. It is in such a combination of signs, more or less developed, that such hearts differ from the normal standard ; it is a difference which is distinct, and the earliest appreciable in the history of rheumatic heart-disease. It cannot be explained by pyrexia, for it may be present when the temperature is normal ; nor by the effect of salicylates, for it is present before treatment has been commenced ; nor in cases of chorea by the movements, for its amount bears no constant relation to the severity of these. It is not merely a part of the debility caused by an illness, for it

is often much more distinct in very mild attacks of rheumatism than in more severe diseases. It is evidently in some way a special result of the rheumatic process. The evidence already given appears to prove that it is independent of pericarditis. It is more difficult to prove the absence of endocarditis, but if any valvulitis at all was present in the above cases it must have been extremely slight, and quite incapable of producing so definite an enlargement of the heart, or one capable of such easy recovery. It seems impossible to avoid the conclusion that in rheumatism there is some toxic action exerted on the cardiac muscle, enfeebling it and causing it to give way before the normal blood-pressure. This explains why the first sound becomes short, the area of dullness increased, and the impulse diffused. The feebler diastolic rebound, causing a weaker suction action in diastole, explains why the pulmonary tension rises, and the pulmonary second becomes accentuated.

Before passing to the more severe rheumatic cases, which we have placed in the third group, we wish to give an example of acute dilatation in a first attack of chorea, which was followed by definite valvulitis.

CASE 6. L. H—, aged 11, admitted into hospital August 19, 1897, under Dr. Lees, for moderate chorea of two weeks' standing.

L. H., aged 11. Chorea, first attack.



No. 1. Aug. 20, 1897. No. 2. Aug. 30, 1897.

! accentuated pulmonary second sound. * systolic murmur. → systolic murmur conducted to axilla. × × diffuse impulse.

August 20. First tracing. Temperature 99°. Impulse external to nipple. Area as shown. First sound short. Sounds spaced. A very faint soft murmur heard internal to the impulse.

This condition continued unchanged for ten days. On the 29th the temperature rose from normal to 99.8°, and a definite musical blowing murmur appeared.

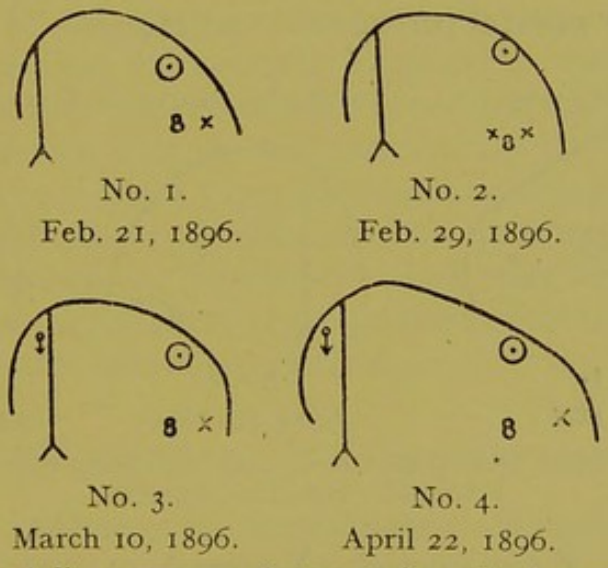
30*th*. Second tracing. Area as shown. The murmur could be traced to the axilla, and all who examined the case agreed that there was now definite valvulitis. When the patient left the hospital a month later, the murmur was still present and audible in the axilla.

GROUP III. *Severe cases of acute rheumatic heart disease, with definite valvulitis and frequently pericarditis.*

We give tracings from two cases as types of these severe attacks.

CASE 7. E. C—, aged 11, admitted into the Hospital for Sick Children, February 20, 1896, under Dr. Penrose, for a severe first attack of chorea. In the out-patient department in the morning no murmur was heard, but later in the day a soft apical murmur appeared.

E. C—, aged 11. Chorea and rheumatic fever, first attack.



No. 1. Feb. 21, 1896. No. 2. Feb. 29, 1896.

No. 3. March 10, 1896. No. 4. April 22, 1896.

* diastolic murmur. 8 to-and-fro mitral murmur. × impulse.

February 21. First tracing. Temperature 101°. Impulse external to nipple. Area as shown. A to-and-fro murmur audible external to the nipple. Loud pulmonary second.

23*rd*. Erythema.

27*th*. Arthritis.

29*th*. Second tracing. Temperature 99°. Area slightly diminished. For some days the aortic second had been short.

March 10. Third tracing. Area no larger than before, though a well-marked aortic diastolic murmur had developed. The rheumatism had quieted down.

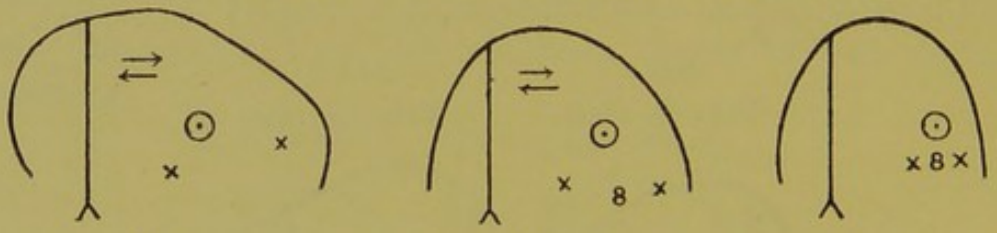
April 22. Fourth tracing. After decided improvement there were now fresh pyrexia and joint pains. Area decidedly increased. Signs of aortic disease less marked.

Eventually the boy recovered sufficiently to leave the hospital, but with marked aortic and mitral regurgitation.

In this case there was no evidence of pericarditis. The increase in the cardiac dullness was most marked when the rheumatism was most active, and it diminished when the rheumatism subsided. With the fresh outburst the area again became enlarged. If the dilatation had been due to the valvular lesions, it would not have varied in this way, but would have steadily and gradually increased until checked by compensatory hypertrophy.

CASE 8. E. B—, aged 8, admitted under Dr. Penrose April 11, 1896, for general pericarditis and chorea.

E. B—, aged 8. Chorea and rheumatic fever, first attack.



No. 1. April 12, 1896. No. 2. April 18, 1896. No. 3. April 29, 1896.

⇄ pericardial friction. × × diffuse impulse.
8 to-and-fro mitral murmur.

April 12. First tracing. Temperature 99°. No definite impulse ; area as shown ; loud general friction. Very ill.

17*th*. Sharp râles over front of left lung.

18*th*. Second tracing. Area diminished ; less friction ; a double murmur at the apex.

29*th*. Third tracing. Remarkable improvement ; chorea almost gone. Area still further diminished. No friction ; double murmur plainly heard.

June 8. Discharged ; only a loud systolic murmur remains ; area still further diminished.

In this case, when the area of cardiac dullness was most extensive, the pericardial friction was loudest and most general. This suggests that there was probably no great excess of fluid in the pericardial cavity. The suggestion is supported by the post-mortem records of fatal cases of rheumatic heart disease. In only 12 out of 150 cases (see Appendix C) is it definitely stated that more than two ounces of fluid were found in the pericardial cavity. By actual experiment on the cadaver we have ascertained that this quantity will not produce anything like the enlargement of the cardiac area often observed during life. Dr. Sibson found that six ounces of fluid were required to distend the pericardium in a boy of nine. If to these facts we add the clinical observation that the area of pulsation, in these cases, is usually extensive and the cardiac sounds fairly loud, we are driven to the conclusion that in the great majority of cases of rheumatic pericarditis the increase in the area of cardiac dullness is mainly due to dilatation. At first sight it might seem that the dilatation is secondary to the pericarditis, but it is much less marked in suppurative than in rheumatic pericarditis, and it is often marked in rheumatism in which no pericarditis exists. We conclude, therefore, that the enfeeblement of the cardiac wall is mainly due to a direct toxic action of the rheumatic poison. However brought about, the dilatation is a most serious addition to the valvulitis or the pericarditis which may accompany it, and takes a very large share in the production of the dangerous symptoms usually attributed to them.

GROUP IV. *The more chronic forms of chorea and rheumatism.*

Careful observation of the clinical course of these more chronic cases, and comparison with the results revealed by post-mortem examination, prove that in them also dilatation of the heart is one of the most important factors. A moderate valve lesion in a child is easily and effectually compensated if no fresh incidence of rheumatism occurs. On the other hand, grave symptoms of cardiac failure in a rheumatic child are almost always accompanied by fresh rheumatic manifestations. In 100 such cases ending fatally (Appendix C) there was evidence (apart from endocarditis) of fresh rheumatism in 86. We lay special stress on this fact, for it indicates that in children the

fatal issue of rheumatic heart disease is not often the mechanical result of damaged valves, as is frequently the case in adults, and that some other explanation of the acute cardiac failure is required. And this is confirmed by the fact that the amount of change in the valves in such cases is usually moderate or slight. The chief cause of the fatal issue is indicated by the analysis of 150 autopsies in Appendix C, in which dilatation of the heart is specially mentioned in 92, while hypertrophy is noted in only 58.

The progress of rheumatism, as seen in hospital, fully supports this view. The cases which end fatally often present, during a course of several months, a series of rheumatic exacerbations, —now nodules, now arthritis, now pericarditis. The heart enlarges immensely, and the enlargement occurs synchronously with the rheumatic exacerbations. When they quiet down it ceases, and the area may even diminish. This enlargement is not a hypertrophy ; the physical signs and the prostration of the patient prove that it is a heart-failure, and therefore a dilatation.

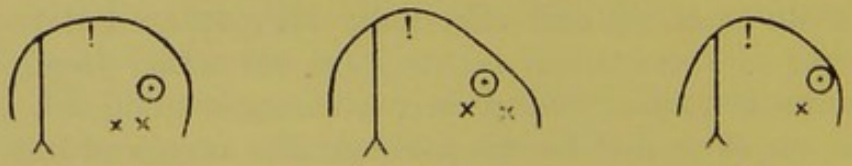
On the other hand, when no fresh rheumatic manifestation occurs, there is rarely any rapid increase of the cardiac area, even though valvulitis exists.

In chronic cases, then, if they are to prove fatal, the course is one of frequent rheumatic manifestations along with acute dilatations of the heart of greater or less severity.

In illustration of the above remarks we now give tracings from two chronic cases.

Case 9. M. P—, aged 9, admitted into the Hospital for Sick Children, October 25, 1895, under Dr. Penrose, for chorea. She remained in the hospital until November 30, then was sent to the Highgate Convalescent Home, much better, but not

M. P—, aged 9. Chronic chorea.



No. 1. Feb. 9, 1896. | No. 2. March 3, 1896. | No. 3. April 21, 1896.

! accentuated pulmonary second sound. × × impulse diffuse.

well. She was readmitted February 6, 1896, with pain in the side, and increase of the chorea, which had never disappeared.

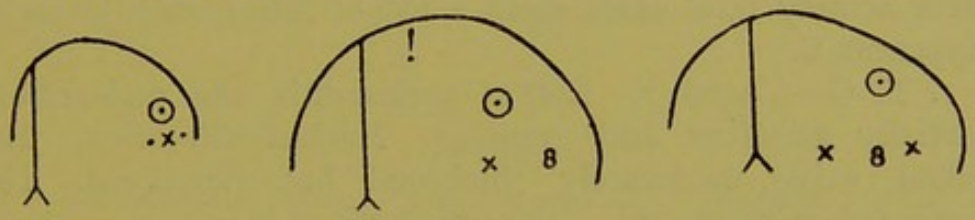
February 9. First tracing. Chorea severe. Area as shown.

March 3. Second tracing. Chorea still severe. A soft murmur now heard internal to nipple. Area further increased.

April 21. Third tracing. Chorea gone, after six months' duration. Area considerably diminished.

Case 10. W. M—, aged 8, admitted into the Hospital for Sick Children, December 4, 1895, under Dr. Penrose for chorea, endocarditis, and doubtful pericarditis ; the attack dated from October.

W. M—, aged 8. Subacute rheumatic fever, second attack.



No. 1. Dec. 5, 1895. No. 2. March 26, 1896. No. 3. April 21, 1896.

! accentuated pulmonary second sound. × impulse.
8 to-and-fro mitral murmur.

December 5. First tracing. Area as shown. Organic mitral murmur and doubtful pericardial friction.

Throughout December and January the chorea persisted, with slight irregular pyrexia ; once in January what appeared to be pericardial friction was heard, and nodules were found. During the whole of February the child lay in bed, pale and speechless, with slight chorea ; more nodules developed, and fresh pyrexia. Several cardiac tracings were taken.

March 26, 1896. Second tracing. Area much enlarged. Nodules still appearing.

During April he began slowly to improve, and the rheumatic symptoms to disappear.

April 21. Third tracing. Area diminishing.

The improvement continued, and he recovered sufficiently to leave the hospital.

Throughout the case all the symptoms pointed to dilatation of the heart, and not to hypertrophy or to pericardial effusion.

It is extremely probable that the pericardium was completely adherent, for in 150 fatal cases, acute and chronic, it was found totally adherent in seventy-seven (see Appendix C). But it is doubtful how far even a completely adherent pericardium is in itself a cause of cardiac dilatation. In the records of St. Mary's Hospital we find thirty-four cases of entire adhesion of the pericardium discovered post mortem at ages between fifty and eighty-seven. (In none of these patients were the kidneys granular.) Eighteen of these patients died from causes unconnected with the heart.

In bringing to a close our series of cardiac tracings, we would again draw attention to the evidence of the frequency and importance of dilatation afforded by the post-mortem records. We give brief notes of the condition found in three acutely fatal cases, from a list of fifteen such given in Appendix C.

1. T. G—, aged 7. Recent pericarditis, the pericardium partially adherent and granular. Marked dilatation. The mitral valve moderately thickened but functional. The aortic valves thickened. The myocardium pale.

2. T. B—, aged 10. Pericarditis with much recent adhesion and a little fluid. Fine granulations on the aortic valves and on the mitral flaps. All the cavities dilated. The muscle granular.

3. H. D—, aged 9. General pericarditis, recent and adhesive. Old vegetations on the mitral, but no stenosis. Aortic valves thickened. General dilatation.

In each of these dilatation is a prominent feature, and valvular changes insignificant.

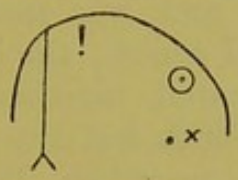
From the clinical records of these cases we find that death is often rapid, frequently sudden and unexpected, and preceded by pallor, collapse, vomiting, delirium, and restlessness, all pointing to grave circulatory failure. Active rheumatism is almost invariably present. Much excess of pericardial fluid is rare. Valvular change is usually moderate. Dilatation is more marked than hypertrophy.

The recognition of rheumatic dilatation may sometimes be of service in the diagnosis of an arthritis of otherwise doubtful nature. In July 1896, a girl aged 11 was admitted into the Hospital for Sick Children under Mr. Morgan, for an acute arthritis of the right hip-joint. No other joint was affected.

The thigh was swollen and excessively painful. Pyrexia was present. Acute tubercular disease of the joint was suspected, but the area of cardiac dullness was enlarged, as seen in the subjoined tracing, and there was a soft systolic murmur external to the apex. Extension was applied and salicylates given. Next day two interphalangeal joints of the toes of the left foot were swollen. The affection was undoubtedly rheumatic, and the child was rapidly and completely cured by salicylates. We are indebted to Mr. Morgan for permission to quote this case.

From the point of view of prognosis, the recognition of acute dilatation is of great importance. The occurrence of a second

Girl aged 11. Rheumatic fever, first attack.



July 1896.

! accentuated pulmonary second sound. × impulse.
* systolic murmur.

attack of rheumatism, attended by an acute dilatation, may entirely upset calculations founded merely on an estimation of the valvular damage remaining from the first attack. The possibility of a fresh rheumatic attack, causing increased dilatation, is by far the most important element in the prognosis.

Finally, with regard to treatment, we would point out that acute dilatation is often the earliest indication of a rheumatic heart affection. If, as we believe, salicylate of soda is a specific for rheumatism, and not a mere allayer of pain, it is clearly of the utmost importance to give this drug in sufficient doses as soon as the earliest indication of the pernicious action of rheumatism on the heart is manifested.

The recognition of dilatation will also make us lay greater stress on the necessity for rest in the treatment both of rheumatism and of chorea. And when the question of the advisability of paracentesis pericardii is being considered, the remembrance of the frequency of marked dilatation and of the rarity of much excess of fluid in the pericardial cavity may save us from a therapeutic disaster which has befallen more than one skilled physician in the past.

APPENDIX A

Observations upon the condition of the heart in forty-five children suffering from surgical ailments of slight severity, and free from any disease of the chest. These observations were made at the Hospital for Sick Children, Great Ormond Street, May to November, 1896.

The exact method adopted was as follows : A tracing of the deep cardiac dullness was made in every case. The child was previously kept in bed for a day at least after admission to the hospital. The dullness was percussed from the left side, the patient lying on the back with the arm abducted and chest quite uncovered. The area was marked out as delineated with a dermatographical pencil ; the impulse, left nipple, and mid-sternum were indicated, together with the costal angle. The condition of the sounds and any peculiarity of the chest or physique were also recorded. Finally, the outline was at once transferred to tracing paper and dated.

The results obtained are as follows :

I. The ages of the children :

Between 11 and 12 years . . .	10 cases
,, 10 ,, 11 ,, . . .	6 ,,
,, 9 ,, 10 ,, . . .	5 ,,
,, 8 ,, 9 ,, . . .	5 ,,
,, 7 ,, 8 ,, . . .	3 ,,
,, 6 ,, 7 ,, . . .	8 ,,
,, 5 ,, 6 ,, . . .	2 ,,
,, 4 ,, 5 ,, . . .	1 case
,, 3 ,, 4 ,, . . .	3 cases
,, 2 and 3 years . . .	1 case
,, 1 ,, 2 ,, . . .	1 ,,
	45

II. The particular surgical ailments :

Early morbus coxæ	5
Hydrocele	3
Rectal polypus	1
Early tubercular knee	2
Congenital torticollis	2

Early spinal caries	1
Radical operations for hernia	1
Cleft palate	4
Rickets	3
Functional affection	1
Tubercular glands	4
Adhesions in elbow-joint	4
Chronic abscess	4
Old excision of knee	1
Lupus of skin	1
Gummata over clavicle	2
Ranula	1
Talipes	2
Nævus	1
Hammer-toe	1
Fracture	1
Total	45

III. Distances from the mid sternum to the nipple.

Ages : 11—12, from $2\frac{1}{4}$ to $3\frac{1}{2}$ inches
10—11, ,, $2\frac{1}{2}$,, 3 ,,
9—10, ,, $2\frac{1}{2}$,, 3 ,,
8— 9, ,, $2\frac{1}{2}$,, 3 ,,
7— 8, ,, $2\frac{1}{2}$,, $2\frac{3}{4}$,,
6— 7, ,, $2\frac{1}{4}$,, $2\frac{3}{4}$,,
5— 6, ,, $2\frac{1}{4}$,, $2\frac{1}{2}$,,
1— 5, ,, $2\frac{1}{4}$,, $2\frac{1}{2}$,,

IV. A line drawn at a right angle to the mid-sternal line at the uppermost limit of the tracing passed through the—

Third rib on the left side in	37 cases.
Second space ,, ,,	7 ,,
Third space ,, ,,	1 case.
	45

V. The distance from the mid-sternum to the furthest limit of the heart to the right :

$\frac{1}{4}$ inch in	2 cases.
$\frac{1}{2}$,,	19 ,,

¾ inch in	13 cases
1 " "	8 "
1¼ inches in	1 case.
Doubtful in	2 cases.
	45

The right limit of the heart is not always easily ascertained, either because the chest is misshapen or because there is considerable emphysema. These difficulties are, however, exceptional; if the chest is misshapen it may be difficult to ascertain any limit of the cardiac dullness.

The right limit of the cardiac dullness in children is normally about one fingerbreadth to the right of the right margin of the sternum, as ascertained by percussion. But as this limit is traced from above downward it tends inward a little toward the middle line, following the curve of the auricle. In the healthy heart this is a difficult point to ascertain. When the heart is dilated it is more easily appreciated, but even then may be difficult to demonstrate with certainty.

VI. The relation of the left limit of the cardiac dullness to the left vertical nipple-line:

Internal to the nipple in	19 cases.
In the nipple line in	18 "
External to the nipple in	8 "
	45

Six of the 8 cases in which the dullness extended outside the nipple line were under six years of age. The exact measurements in the eight cases were:

¼ inch in	4
⅜ "	2
½ "	2
	8

In 3 of these cases the children appeared normal, in 3 the chest was noted as small and narrow, in 2 the children were weak and delicate.

It should be stated that in several cases a small, narrow chest was noted, but the left limit was internal to the nipple-line.

VII. The relation of the impulse to the cardiac dullness. This is often considerably internal to the left limit of the cardiac dullness ;

Thus, of 25 cases, in 17 it was internal to this left limit, in 2 it was traced outward as far as the limit, in 6 it was absent to touch.

VIII. The sounds.

The first sound was usually distinctly longer than the second sound. The second sound to the left of the sternum at the base was usually louder than the second sound in the second right space.

In twelve cases the greater loudness of the pulmonary second sound was especially noted.

IX. Irregularity of the heart was exceptional.

X. Bruits were found in some cases.

In 10 an occasional soft systolic murmur was heard in the fourth space just to the left of the sternum.

In 6 a systolic murmur was heard at the base on the left side.

APPENDIX B

Observations upon the hearts of 35 healthy public-schoolboys between the ages of twelve and fourteen.

We realised that cases in the surgical wards of an hospital, though free from chest affections, are not perfectly healthy children. We have accordingly supplemented the results given in Appendix A with the following observations upon healthy schoolboys at Marlborough College. We are much indebted for permission to Dr. Penny, Medical Officer to the school.

In these cases tracings were not taken, but the distances were noted as each cardiac area was percussed. The order of examination, as in previous cases, was firstly, palpation ; secondly, percussion ; thirdly auscultation. The same posture, namely, the supine with the left arm abducted, was adopted as in the previous investigations in Appendix A.

The results obtained were as follows :

I. The ages : between twelve and thirteen years, 4 ; between thirteen and fourteen years, 31.

II. The action of the heart was regular, except in the case of one nervous boy. In this case the irregularity soon passed off.

III. The position of the impulse in relation to the vertical nipple-line and to the ribs :

In the fifth space in . .	23 cases
At the fifth rib in . . .	6 ,,
In the fourth space in . .	4 ,,
Not localised in . . .	2 ,,

The impulse was internal to the vertical nipple-line in 32 cases, and frequently considerably so.

Of the 3 cases in which the impulse was felt in the vertical nipple-line, in 1 case the boy was delicate and in the doctor's house, though in good health at the time.

Case 2 and Case 3 had suffered from influenza six weeks before. This fact was of especial interest, because the condition of the heart had been ascertained in entire ignorance of this history of influenza.

IV. The deep cardiac dullness.

(A) The left limit : in these boys with well-formed chests this area was obtained with considerable ease.

(*a*) In 21 cases the left limit was about one inch internal to the nipple.

(*b*) In 7 cases it reached a vertical line through the inner margin of the areola.

(*c*) In 5 cases it reached the vertical nipple-line.

(*d*) In 2 cases it reached external to the vertical nipple-line.

i. Of these two latter cases, in one limit extended $\frac{1}{4}$ inch external, in one the limit extended 1 inch external.

One of these boys was the delicate boy already mentioned, and in his case there were also soft systolic murmurs at the base and apex.

The other boy had suffered from an attack of influenza six weeks previously ; he had also a soft systolic murmur in the fourth space internal to the nipple.

ii. Of the 5 cases in which the dullness reached the vertical nipple-line, in each there was a soft systolic murmur internal to the nipple.

iii. Of the 7 cases in which the dullness extended almost to the vertical nipple-line, in four there was a soft systolic murmur

internal to the nipple, and in one the first sound was slightly blurred.

iv. Of the 21 cases in which the dullness at its left limit was distinctly internal to the vertical nipple-line, in only two a soft systolic murmur was noted internal to the nipple.

(B) The right limit : in 4 cases hyper-resonance prevented the limit being defined.

In 2 cases the limit was $1\frac{1}{4}$ inches from the mid-sternum.

In 29 cases the limit was from $\frac{3}{4}$ to 1 inch to the right of the mid-sternum.

(C) The upward limit to the left of the sternum.

The third rib in 34 cases, the second space in 1 case.

V. The sounds.

In 5 cases the first sound at the apex was rather short.

The second sound over the left second space was almost invariably louder than over the right second space, but both were well defined and sharp.

In the cases with soft systolic murmurs the second sound to the left was especially louder than that to the right.

VI. Murmurs. There was not a musical murmur in any of these cases ; they were all soft blowing murmurs, some diminished by the erect posture.

The situation in which they were heard most frequently and at their loudest was in the fourth space close to the left margin of the sternum. This murmur became fainter when traced to the nipple, and in only one case was heard external to it, and then very faintly indeed. It also became fainter when traced toward the base.

The exact numbers in which murmurs were heard when classified are as follows :

Blowing murmurs were heard in 15 cases.

In 9 cases out of this number the murmur was best heard in the fourth space on the left side.

In 6 cases the murmur was basal.

In three of the 15 cases a murmur was heard in both situations.

In each of these three cases the cardiac dullness was more extensive than usual.

APPENDIX C

An analysis of 150 *fatal cases of rheumatic morbus cordis in children, derived from the post-mortem records of the Hospital for Sick Children, Great Ormond Street, and St. Mary's Hospital.*

The analysis contains observations upon the following points :

1. The sex incidence (150 cases).
2. The age incidence (150 cases).
3. The number of fatal first attacks (115 cases).
4. The relation of the attacks to scarlet fever (100 cases).
5. The season in which the fatal attack commenced (150 cases).
6. The condition of the pericardium (150 cases).
   (*a*) As to adhesion.
   (*b*) As to fluid.
7. The condition of the myocardium (150 cases).
8. The condition of the mitral valve (150 cases).
9. The condition of the aortic valve (150 cases).
10. The condition of the tricuspid valve (150 cases).
11. The condition of the pulmonary valve (100 cases).
12. The combination of valvular lesions (150 cases).
13. The evidence of fresh rheumatic manifestations in the fatal illness (150 cases).
14. The frequency of nodules in fatal cases (87 cases).
15. The frequency of pericardial friction toward the end of the illness (100 cases).
16. The frequency of marked dropsy (100 cases).
17. The condition of the heart in 25 cases with marked dropsy.
18. The frequency of sudden death as the termination of the illness (100 cases).
19. The frequency of chorea in the last illness (100 cases).
20. The condition of the heart *post-mortem* in fifteen acute attacks of rheumatic fever rapidly fatal.

I. The sex :

Females . . .	88	= 59 per cent.
Males . . .	62	= 41 ,,

II. The age incidence :

Up to $3\frac{1}{2}$ years of age		1 case	=	0.6 per cent.
$3\frac{1}{2}$,, $4\frac{1}{2}$	,, ,,	6 cases	=	3.9 ,,
$4\frac{1}{2}$,, $5\frac{1}{2}$	,, ,,	11 ,,	=	7.4 ,,
$5\frac{1}{2}$,, $6\frac{1}{2}$	,, ,,	14 ,,	=	9.4 ,,
$6\frac{1}{2}$,, $7\frac{1}{2}$	,, ,,	19 ,,	=	12.7 ,,
$7\frac{1}{2}$,, $8\frac{1}{2}$	,, ,,	19 ,,	=	12.7 ,,
$8\frac{1}{2}$,, $9\frac{1}{2}$	,, ,,	23 ,,	=	15.3 ,,
$9\frac{1}{2}$,, $10\frac{1}{2}$	,, ,,	30 ,,	=	20 ,,
$10\frac{1}{2}$,, $11\frac{1}{2}$	,, ,,	18 ,,	=	12 ,,
$11\frac{1}{2}$,, 12	,, ,,	9 ,,	=	6 ,,
		150		

The maximum is reached at the tenth year.

III. Fatal first attacks.

It is not always easy to be certain that the attack which proved fatal was really the first ; but out of 115 fatal cases 35 were apparently first attacks.

IV. The relation (if any) to scarlet fever.

Of 100 cases of fatal rheumatism, in which the occurrence or non-occurrence of scarlet fever was noted, in only six did there seem to be any possibility of a relation between the two diseases. The relation in these six cases was as follows :

In one, scarlet fever occurred three years before, "child never well since."

In one, scarlet fever occurred ten weeks before the symptoms of rheumatic fever.

In one, scarlet fever occurring two years before was at once followed by an attack of rheumatic fever.

In one, scarlet fever was followed in a week by rheumatic fever.

In one, scarlet fever was followed in a month by rheumatic fever.

In one, scarlet fever was "followed shortly" by rheumatic fever.

It appears, therefore, that rheumatic fever in the great majority of cases arises quite apart from scarlet fever.

V. The season in which the fatal attack commenced.

This analysis is founded on the appearance of the first

symptoms of the illness. This date must be open to some doubt, but in a large number of observations should be fairly accurate.

Of 150 cases 67 commenced in the autumn
33 ,, spring.
30 ,, winter.
20 ,, summer.

That is, 66 per cent commenced in autumn and spring.
34 ,, ,, winter and summer.

VI. The condition of the pericardium in 150 cases :

(A) As to adhesions :

i. More or less adherent in 113 = 75 per cent.
ii. Not adherent in . . 37 = 25 ,,

i. In the cases (113 in number) of adhesion—

(*a*) In 77 the adhesion was general.
(*b*) In 36 it was partial.

(*a*) In the 77 cases of total adhesion—
19 were stated to be old adhesions.
18 ,, ,, recent adhesions.
40 were of doubtful age.

(*b*) In the 36 cases of partial adhesion—
6 were described as adherent.
8 ,, ,, much adherent.
13 ,, ,, partly adherent.
9 showed recent granular pericarditis.

ii. In the 37 cases described as not adherent, in only 9 was the pericardium definitely stated to be healthy.

(B) As to fluid in the pericardial cavity :

In 38 cases out of 150 = 25 per cent, a special note was made of fluid in the following terms :

" Little " or " very little " . . in 9 cases.
" Some " . . . . . in 3 ,,
" Under one ounce " . . . in 4 ,,
" Between one and two ounces " . in 6 ,,
" Between two and three ounces " in 6 ,,
" Five ounces " . . . . in 1 case.
" Six ounces " . . . . in 1 ,,
" Excess " . . . . in 4 cases.
" Much excess " . . in 4 ,,

38

Thus in only 12 out of 150 cases of fatal rheumatic fever is it definitely stated that more than *two* ounces of fluid were in the pericardial cavity, and in only 6 cases more than *three* ounces.

It is worthy of careful note that much fluid in the pericardium is rarely found after death from rheumatic pericarditis.

VII. The condition of the myocardium in 150 cases :

(A) As to change in appearance, macrosopic and microscopic.

In 34 cases there is special mention of change—that is in 23 per cent—in the following terms :

"Soft and pale" . . .	in 15 cases.
"Tough and fibroid" . .	in 8 ,,
"Fatty"	in 4 ,,
"Opaque"	in 1 case.
"Striæ indistinct" . . .	in 1 ,,
"Myocardial change" . .	in 5 cases.

These numbers can only be looked upon as evidence that myocardial change occurs. They are no gauge of the frequency of its occurrence. In many of the cases microscopic examinations of the cardiac walls were not made.

(B) The condition of the myocardium as to hypertrophy and dilatation in 150 cases.

Hypertrophy is especially mentioned in 58 cases in the following terms :

i. "Great," "much," or "general" hypertrophy in 18 cases. In two of these the left ventricle was especially affected.

ii. "Hypertrophy" in 29 cases.
Of these, in 7 the left ventricle especially.
in 1 the right ventricle especially.

ii. "Some hypertrophy" in 8 cases.

iv. "A little hypertrophy" in 3 cases.

Dilatation is especially mentioned in 92 cases. Thus :

i. "Marked," "much," or "general" dilatation in 56.
Of these—

(*a*) "General dilatation" . .	in 19 cases.
(*b*) "Marked" and "much" .	in 24 ,,
(*c*) "Enormous" . . .	in 1 case.
(*d*) "Great"	in 5 cases.
(*e*) "Of both ventricles" . .	in 5 ,,

(*f*) "Of the left ventricle" . . in 1 case.
(*g*) "Of the right ventricle" . in 1 ,,

ii. "Dilatation especially" in 4 cases.
iii. "Dilatation" in 24 cases.
iv. "Some dilatation" in 6 cases.
v. "Walls thin" in 2 cases.

In forming from these data an opinion as to the frequency and relative amount of hypertrophy and dilatation respectively, it must be remembered that in some of the cases no definite statement is made; that in others a preponderance of hypertrophy may have caused the omission of any statement as to dilatation, or *vice versa*; finally, that the very existence of slight degrees of hypertrophy or dilatation may be differently judged by different observers. For these reasons the numbers have not been reduced to percentages, but the general tendency of the facts recorded seems to indicate that dilatation is both more frequent and more marked than hypertrophy. For while the latter is noted in 58 cases the former is noted in 92, and in 56 of these it was evidently a striking fact.

VIII. The condition of the mitral valve in 150 cases. Affected in 149.

The following are the descriptions of the changes:

(1)	"Marked mitral stenosis" in . .	9 cases.
(2)	"Marked mitral regurgitation" in .	11 ,,
(3)	"Much thickening and puckering" in	8 ,,
(4)	"Mitral regurgitation" / "Mitral stenosis" / "Double mitral" in . .	41 ,,
(5)	"Some thickening" in . . .	45 ,,
(6)	"Numerous vegetations" in . .	4 ,,
(7)	"Vegetations and small deposits" in	31 ,,
		149

We may conclude that some affection of the mitral valve is almost invariably present in fatal rheumatism in children; that in about one half of the fatal cases the lesion is slight, in about one fifth great; that thickening of the mitral valve is common, but that a marked degree of stenosis is rare in children under twelve.

IX. The condition of the aortic valves in 150 cases. The valve was affected in 51 cases = 34 per cent.

The details are as follows :

(1)	" Much aortic regurgitation " in .	1 case.
(2)	" Definite aortic regurgitation " in .	4 cases.
(3)	" Definite aortic stenosis " in . .	4 ,,
(4)	" Vegetations and beading " in . .	19 ,,
(5)	" Thickening " in . . .	18 ,,
(6)	" Aortic valves affected " in . .	5 ,,
		51

Slight change is the rule.

X. The condition of the tricuspid valve in 150 cases. This valve was affected in 36 cases = 24 per cent.

The details are as follows :

" Marked stenosis " in . . .	1 case.
" Vegetations " in	15 cases.
" Thickening " in	20 ,,

Again, if the valve is affected at all, slight change is the rule.

XI. The condition of the pulmonary valve in 100 cases. This was affected in 4 = 4 per cent, as follows :

" Thickened "	in 3 cases.
" Dilated "	in 1 case.

XII. The frequency of a combination of valvular lesions in 149 cases.

(*a*) In 4 cases at least all the four valves were affected.

(*b*) In 32 cases the mitral, aortic, and tricuspid valves were affected.

(*c*) In 15 the mitral and aortic valves were affected.

(*d*) In 98 the mitral valve only was affected.

XIII. The evidence of fresh rheumatic manifestations in 100 fatal cases.

The evidence relied upon consists of chorea, pericarditis, nodules, arthritis, and erythema occurring during the fatal illness.

The possibility of fresh endocarditis supervening upon old is not taken into account because of the difficulties in proving its occurrence.

Eighty-six out of 100 cases showed undoubted manifestations of recent rheumatism.

Of the remainder = 14 per cent.—

Three cases were doubtful.

Two cases died with much cardiac dilatation.

One case died with cerebral hæmorrhage.

One case died, and total adhesion of the pericardium and much endocarditis were found.

Two cases died with "marked mitral stenosis."

Two cases died with "marked mitral regurgitation."

Two cases died, and a totally adherent pericardium was found.

In one case there was a history of three years' gradual failure.

These figures are worthy of especial note, for they point strongly to this fact, that cardiac break-down in children with damaged hearts is mainly due to a fresh rheumatic attack, not to overstrain.

XIV. The frequency of nodules in fatal cases since 1879.

Eighty-seven cases are recorded since that date. In 47 of these nodules were present, and in 8 their occurrence was doubtful. That is, nodules are found in about 54 per cent of fatal cases.

This result probably rather under-estimates the frequency of their occurrence.

XV. The frequency of pericardial friction toward the end of the fatal illness.

Of 100 cases, in 55 friction was noted, in 15 it was doubtful, and in 30 it was not mentioned.

XVI. The frequency of marked dropsy.

Observations are taken from 100 cases.

In 25 cases it was described as "much" or "considerable."

In these cases—

(*a*) It was of long standing in 8 cases.

(*b*) It was of some standing in 8 cases.

(*c*) Quite recent in 9 cases.

XVII. The condition of the heart as found post-mortem in these 25 cases of marked dropsy.

Group A. The 8 cases of long standing.

(1) In 3 there was marked mitral stenosis.

(2) In 1 there was thickening of the mitral valve, and the pericardium was ¼ of an inch thick.

(3) In 1 there was mitral stenosis and incompetence and aortic regurgitation.

4) In 1 there was marked mitral and tricuspid incompetence.

(5) In 2 mitral incompetence.

Group B. Eight cases of dropsy of some standing.

(1) In 1 there was marked mitral stenosis.

(2) In 3 there was marked mitral incompetence.

(3) In 2 the heart was described as fibroid, and the pericardium was totally adherent.

(4) In 1 the chordæ tendineæ of the mitral valve were described as much thickened.

(5) In 1 the pericardium was adherent to the chest wall.

The chief feature in these cases of marked dropsy is the occurrence of decided valvular disease.

XVIII. The frequency of sudden death in 100 cases; by this is meant the occurrence of death unexpectedly in the last illness. This occurred in 33 cases, as follows:

(*a*) "Very sudden" in 11. In three of these myocardial change was noted.

In two of these cases it is expressly stated that just before the sudden end the children had been improving.

(*b*) Attacks of collapse or much vomiting, then a sudden end, in 8 cases.

(*c*) "Sudden" in 8 cases.

(*d*) "Rather sudden" in 6 cases.

In many more cases there was severe vomiting some days before death.

XIX. Fatal cases in which chorea was a prominent symptom. Some of these cases had other evidences of severe rheumatism at the time of admission, others rapidly developed them. Twenty cases are recorded here, and 14 of these were first attacks of rheumatism.

This is very striking confirmation of the close association of rheumatism and chorea—rheumatism, too, which may prove to be of the most virulent type.

XX. Brief abstracts of the post-mortem appearances of the heart in fifteen acute cases rapidly fatal.

CASE 1. E. K—, aged 11. Chorea and recent rheumatic fever.

Post-mortem. The pericardium contained a considerable amount of fluid, with flakes of lymph. The heart weighed 8¼ ounces. There were rows of bead-like granulations on the mitral, aortic, and tricuspid valves.

CASE 2. M. W—, aged 9. Chorea, first attack, and rheumatic fever.

Post-mortem. Recent granular pericarditis, a little fluid, much dilatation of all the cavities, and recent vegetations on the mitral and aortic valves. The heart muscle was flabby.

CASE 3. G. K—, aged 11. Acute rheumatic fever.

Post-mortem. Recent pericarditis with extensive lymph-shreds, dilatation, but very little hypertrophy of the ventricle. The mitral valve thickened and fringed with vegetations. Minute vegetations on the aortic and tricuspid flaps.

CASE 4. F. S—, aged 3. Acute rheumatic fever.

Post-mortem. Recent pericarditis; a few drachms of fluid in the sac. Much general dilatation. The mitral valve dilated, with recent vegetations on the mitral and tricuspid flaps.

CASE 5. J. B—, aged 10. Acute rheumatic fever.

Post mortem. Pericarditis with much recent adhesion and a little fluid; fine aortic granulations, and some fine granules on the mitral flaps. All the cavities dilated, muscle granular.

CASE 6. F. J—, aged 4. Acute rheumatic fever.

Post-mortem. Recent pericarditis; a little fluid. Much dilatation of all the cavities. Some mitral thickening and a few vegetations on the aortic valves.

CASE 7. P. W—, aged 3½. Acute rheumatic fever.

Post-mortem. Recent pericarditis with adhesion; one ounce of fluid in the sac. Heart dilated. Slight vegetations on the tricuspid flaps. Numerous fine vegetations on the mitral.

CASE 8. M. M—, aged 6½. Acute rheumatic fever.

Post-mortem. Recent general adhesive pericarditis. Two drachms of fluid in the sac. General adhesive pericarditis.

General dilatation with a little hypertrophy of the left ventricle. Some old thickening of the mitral valve. Slight aortic puckering.

CASE 9. H. W—, aged 9. Acute rheumatic fever.

Post-mortem. Pericarditis, general, recent, and adhesive. Old vegetations on the mitral, but no stenosis. The aortic valves thickened ; general dilatation of cavities.

CASE 10. M. W—, aged 8. Acute rheumatic fever.

Post-mortem. General pericarditis. Some fluid in the pericardial sac. Dilatation of the ventricles. Some hypertrophy. Beading of the mitral valve.

CASE 11. C. S—, aged 8. Rheumatic fever and chorea.

Post-mortem. Recent pericarditis, general and adhesive. Small vegetations on the aortic and mitral valves ; heart enlarged.

CASE 12. F. B—, aged 8. Acute rheumatic fever.

Post-mortem. Pericardium totally adherent ; recent adhesions. General dilatation, little valvular change.

CASE 13. G. N—, aged 6. Acute rheumatic fever.

Post-mortem. The pericardium contained two ounces and a half of fluid with recent flakes. Much dilatation, and dilatation of the valve orifices. Little valvular change. Fatty changes in the heart muscle.

CASE 14. H. B—, aged 11. Acute rheumatic fever.

Post-mortem. Pericarditis, with recent adhesions to the left ventricle of the heart. Some mitral thickening, much general dilatation, and dilatation of the valve rings. Fatty changes in the heart muscle.

CASE 15. A. B—, aged 11. Acute rheumatic fever.

Post-mortem. The pericardium contained one ounce and a half of fluid. Some adhesions, no lymph. Mitral and tricuspid beading.

PAPER NO. II

A CASE OF RHEUMATIC PERICARDITIS AND EXTREME DILATATION OF THE HEART

WITH AN

INVESTIGATION INTO THE MICROSCOPY OF RHEUMATIC HEART DISEASE

COMMUNICATED BY DR. NORMAN MOORE

(From vol. 82 of the *Medico-Chirurgical Transactions.*)

1899

The facts determined in the preceding paper led to an enquiry into the pathological anatomy of the myocardium in rheumatic carditis. Some of the results are recorded in this paper. Subsequent developments following on the researches of Kent-Hughes, Aschoff, Tawara, and others upon the auriculo-ventricular bundle, and the important writings of Dr. James Mackenzie and his pupils in this country, and of many others on the Continent, have made these results of more importance than we realised.

There will be found in this paper clear evidence of the focal nature of the myocardial changes, which at this time we fully appreciated. Fig. No. 2 shows the submiliary nodule, the importance of which and of the cells contained within it have been brought into prominence by Aschoff, Tawara, and Carey Coombs.

The pathological changes that are described in this paper brought further support to the view that acute rheumatism was of infective origin, but we did not recognise at this time the importance of the minute structure of the focal lesions or their bearing upon the production of cardiac irregularities.

THIS case, which was under the care of Dr. Sidney Phillips, affords both clinical and pathological evidence in support of the statements made by Dr. Lees and Dr. Poynton in two papers read before this Society in June 1898. The first, by Dr. Lees, emphasised the importance of acute dilatation of the heart in rheumatic fever; the second, a joint paper, dwelt upon the frequency of its occurrence in the rheumatism and chorea of childhood.

These views were supported by clinical observations extending over a considerable period of time, and some of the results obtained were illustrated by cardiac tracings thrown on the screen by a lantern. Though personally assured of the truth of the clinical investigation, they felt it necessary to adduce pathological evidence in its support. This was to some extent supplied in an appendix to the papers, by an analysis of 150 cases of fatal rheumatic fever in children under twelve years of age.

In the discussion that followed, the great size of some of the cardiac tracings was criticised. Dr. Ewart, accepted in part the frequency of a considerable increase of the præcordial dullness, but considered the explanation to be an evanescent pericardial effusion.

This case is now brought forward because it deals to some extent with these difficulties, and demonstrates clearly the extreme dilatation that may occur in rheumatic pericarditis with no fluid in the pericardium and practically no valvular disease. The results of the microscopic investigations of the heart, which have been made in this case, seem to indicate clearly a morbid condition of its muscular structure, which goes far to explain the great dilatation.

The case is an example of aggravated cardiac rheumatism, minor degrees of which are of common occurrence. There will be, therefore, no need for lengthy clinical details, and those facts which are concerned with the condition of the heart will alone be described.

Arthur G—, aged 15, was admitted to St. Mary's Hospital on August 25, 1898, for shortness of breath. In December 1897, he passed through an attack of rheumatic fever in which several joints were swollen and very painful, but for which he did not keep his bed. In February 1898, he had another attack of rheumatic fever, which lasted for two months. Since this last attack he had suffered from occasional pains over the heart on exertion. Two days previous to his admission to the hospital a small nodule appeared over the right patella.

On admission, on August 25, his temperature was 100° F., pulse 120, and respirations 30 ; he was very pale and emaciated. The cardiac area was increased, the limits being *one* finger-breadth to the right of the right sternal margin, and *one and a half* to the left of the vertical nipple line ; upward, the limit was

the second left intercostal space. The action of the heart was excited, but no pericardial friction was detected. At the apex there was a loud, harsh, systolic murmur conducted to the axilla, and at the base an accentuated pulmonary second sound. The next day pericardial friction was heard, and this on the following days became loud and general. Upon August 30 the area of cardiac dullness had increased, extending now *two* finger-breadths instead of *one*, to the right of the right sternal margin, and still *one and a half* beyond the left vertical nipple line. The loud friction quite obscured the murmur. Upon September 2 the friction was not so loud, but the cardiac dullness reached the *right nipple line* and extended *two* finger-breadths outside the left nipple line. Upon September 3 the friction was loud and general, and the cardiac dullness extended *one finger-breadth beyond* the right vertical nipple line, and about *three* beyond the left. There was dullness in the fifth right intercostal space (Dr. Rotch's sign). Even with the greatest care, it was impossible to detect any curving inward of the right margin of the cardiac dullness at its lower limit. Over the front of the chest there was doubtful pleural friction on both sides. Upon September 7 the dullness extended *one inch* beyond the right vertical nipple line, and there was systolic retraction of the right intercostal spaces. Pericardial friction was still well marked. The liver extended two inches below the costal margin. Cough, vomiting, restlessness, and all the signs of acute cardiac failure were apparent, and the patient died the following day. The temperature since the day of admission had never risen above 99.5°.

The necropsy was made twenty-four hours after death. During life the areas of cardiac dullness had been confirmed by Dr. A. G. Butler, Dr. Phillips's house physician. After death the dullness was verified as external to the right nipple, and far outside the left. This was also confirmed by a post-mortem assistant. Though the loud, general, and continuous pericardial friction did not suggest a large effusion, there seemed every probability that there would be a distinct increase in the amount of fluid, and the chest wall was removed with especial care, in order to obtain some of this fluid in Pasteur pipettes for bacteriological purposes. The pericardium was however, generally adherent, and the enlargement almost entirely due to the dilated heart, and, to a very minor extent, to the thicken-

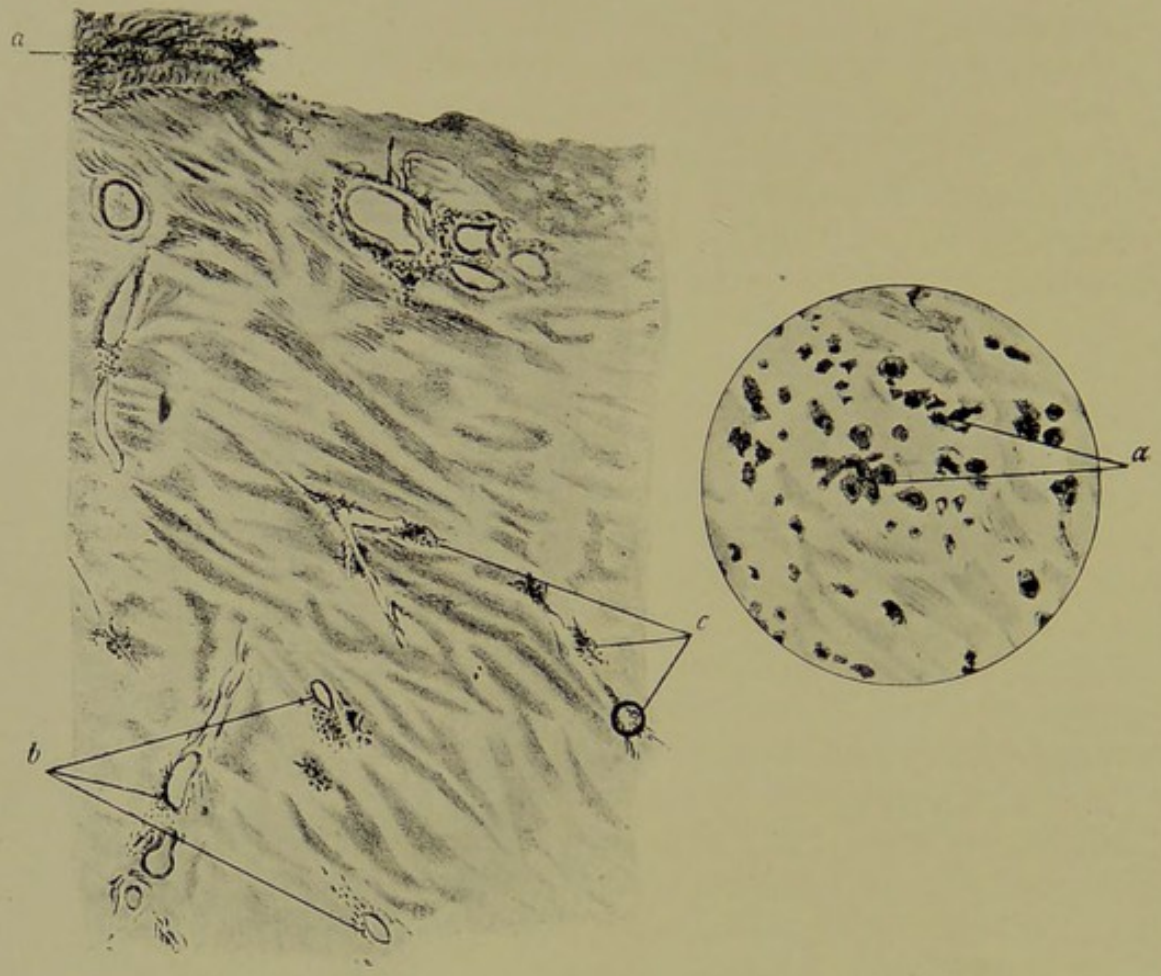


FIG. 1 FIG. 2

FIG. 1. A section through the pericardium and wall of the left ventricle of a case of acute rheumatic pericarditis. (*a*) Inflamed pericardium; (*b*) and (*c*) foci of cellular exudation spreading from the blood-vessels.

FIG. 2. One of the foci under high magnification. (*a*) points to the cellular exudation between the muscle-fibres, now known as the "Submiliary Nodule."

ing of the pericardium. The area of dullness to the right of the sternum was due to the greatly dilated right auricle. In front, over a limited area, the pericardial adhesions were firm, but at the sides and behind the adhesions were quite recent, and the pericardium in places swollen to the thickness of half an inch. The recent adhesions were in the form of flakes of lymph, in the interstices of which was a little fluid. The two lungs were pushed aside by the immense heart, and the pleuræ were adherent to the pericardium by recent adhesions. The valvular changes were extremely slight, consisting only in some thickening of the mitral segments which did not cause any stenosis. There was no recent valvular disease. The valve rings were dilated, and the cavities of the heart crammed with pale and dark clot, and in the right auricular appendix the clot was found firmly adherent. Both ventricles seemed slightly hypertrophied. The weight of the heart with the pericardium, but empty of blood, was twenty-six ounces. The muscle was streaked with pale striæ, and had on section a pale purple colour. The other viscera showed changes compatible with a recent and acute cardiac failure.

Numerous sections of the pericardium, heart-wall, blood-clot, and nodules were made. The salient points of these will be described. In addition, sections were taken from other examples of rheumatic heart disease, from a case of advanced alcoholism, Addison's disease, and from a case of cardiac fibrosis. These appear to support the views that are held in this paper, and they will be alluded to as the points they illustrate are considered.

In the case above described, a section through the inflamed pericardium showed extreme vascular dilatation and plastic inflammatory exudation into the pericardial cavity. In the wall of the left ventricle there was a similar but slighter capillary distension, and both under the pericardium and far away from it there was a free exudation of small cells between the muscle-fibres. The muscle itself showed great loss in striation, and many of the fibres showed granules not of a fatty nature in the proximity of the nucleus. In sections through the right ventricle, the most striking changes were beneath the pericardium, but they were visible throughout the entire thickness of the ventricle wall. Another series of sections were fixed in Hermann's osmic fluid. Both beneath the pericardium and

throughout the heart-wall there was fatty degeneration of the muscle-fibres. Sections through the right auricular appendix and ante-mortem clot showed externally pericarditis, then hyaline change in the muscle, and coagulation necrosis in the blood-clot.

Thus it will be seen that the changes in the cardiac wall were very general, affecting muscle, vessels, and interstitial tissues. The early commencement of the interstitial changes are, however, better seen in some sections taken from another case of pericarditis. In this case, published in the *Lancet*, July 23, 1898, death was caused by a rare complication, extensive thrombosis of the large veins of the neck and upper extremities. The pericardial friction in this case was detected only the day before death. The sections show numerous foci of inflammatory exudation scattered through the wall of the ventricle, and were not localised to that part of the myocardium lying immediately beneath the pericardium. In this case also during life there was great dilatation.

Though these morbid changes are distinct and easily recognisable, the parenchymatous changes are by no means as profound in these rheumatic hearts as in some other conditions. Thus, in some sections taken from the left ventricle of a case of advanced alcoholism, it is difficult to recognise at first sight the muscular tissue, because the changes are so extreme. Yet during life it was especially noted that there was no appreciable dilatation, a point to which allusion will be made later. Again, though the alterations in the interstitial tissues of the heart are quite definite in these acute cases of rheumatism, they are more extreme in the sections of a fibroid heart taken from a case that terminated in the sudden death of the patient. Yet though the microscopic changes in these fatal cases of acute rheumatism were not extreme, they were general and diffuse.

The sections next described are also from a case of cardiac rheumatism, but with a different clinical history. They were taken from the left ventricle of a man aged twenty-nine. He had suffered in childhood from rheumatic fever, and five years before his death had been known to have organic, mitral, and aortic disease. He finally died in another attack of rheumatism, complicated with pneumonia. These sections show fibrosis of the ventricle — evidence of the previous

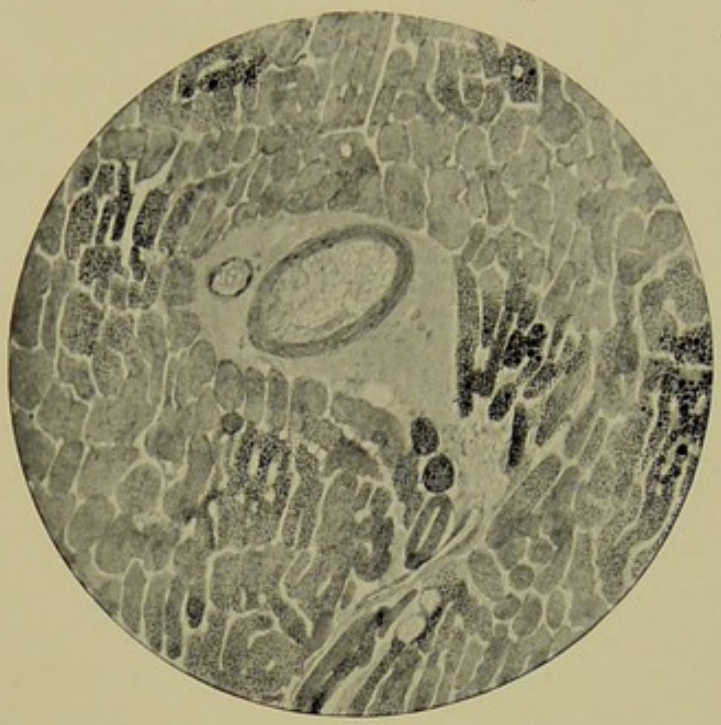


FIG. 3

Rheumatic myocarditis showing fatty change in the muscular fibres in the neighbourhood of a blood capillary. The fat-droplets are stained black with osmic acid.

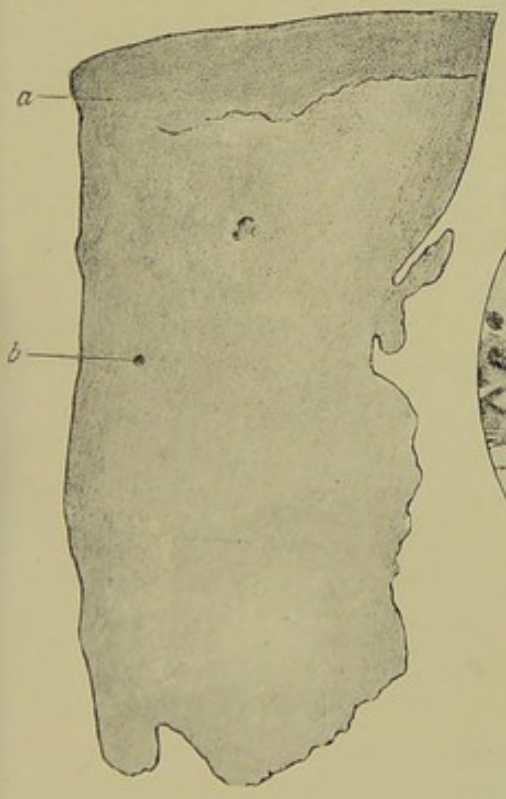


FIG. 4

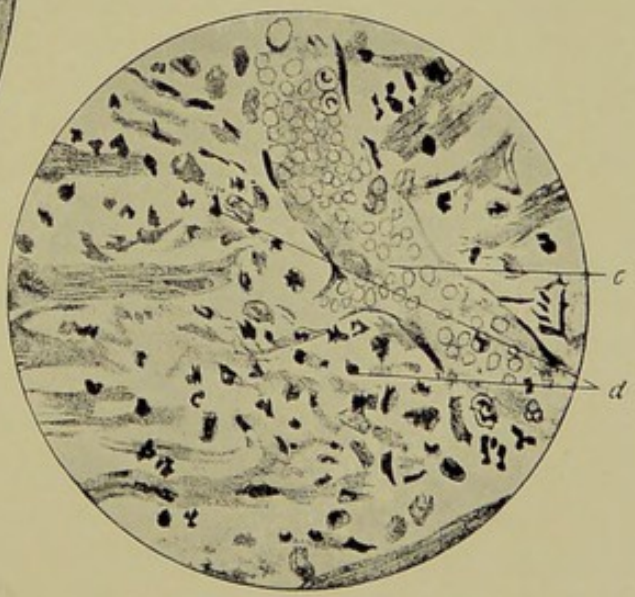


FIG. 5

FIG. 4. A diagram of the pericardium and wall of the left ventricle. (*a*) Pericardium; (*b*) indicates the position in the ventricle from which the sketch of the adjoining figure was taken.

FIG. 5. (*c*) Blood capillary cut longitudinally; (*d*) cellular exudation between the muscular fibres.

rheumatic attacks, and in addition multiple foci of small-celled exudation scattered through the ventricle—evidence of the recent illness. It is noteworthy that macroscopically this muscle appeared natural, and that there was not any recent valvular disease or pericarditis, but an adherent pericardium of old standing.

It remains now to consider shortly the bearing of these details upon the question of rheumatic dilatation. The case itself proves conclusively that great dilatation, greater than any that was represented in the tracings in the paper on dilatation of the heart in rheumatism, may occur in rheumatic fever with plastic pericarditis, but without valvular disease of any appreciable severity. It also proves that Dr. Rotch's sign may be obtained when there is no pericardial effusion. Such a case as this, taken together with the previous clinical evidence makes it probable that dilatation of less degree may occur without pericarditis, and that the myocardial changes are not a *sequela* of the pericarditis. If pericarditis is present the changes are concurrent, and they probably occur in the myocardium independently of any pericarditis.

It is usually considered that the pericarditis is the starting-point of the myocardial inflammation, and is the explanation of the dilatation and severe symptoms that appear in the worst cases of cardiac rheumatism. Several observers have, however, held that the myo- and peri-cardial changes are concurrent, and part of the same rheumatic process. Thus, Dr. Cheadle, when writing of chronic pericarditis, suggests this in the Harveian Lectures on the "Rheumatic State in Childhood" in 1888, and the same opinion was expressed by the late Dr. Sturges in the term rheumatic carditis. Dr. Theodore Fisher, both at the meeting of this Society in June and again at Edinburgh in July, stated that he had observed pathological changes in the myocardium apart from any pericarditis.

The microscopic sections, support the view that when pericarditis is present, the myocardium is also affected concurrently, for the changes in the heart-wall commence by numerous scattered foci, some of them far from the pericardium, and the changes in the muscle are general.

This view is also supported by the recent advances of pathology, especially in the investigation of cardiac muscle, for these emphasise the fact that micro-organisms gaining

access to the body give rise to toxines which circulate in the system. These, doubtless, by delicate chemical reactions injure the tissues, and usually have, to some extent, a specific action on certain classes of tissues. When after death from rheumatic morbus cordis, acute changes are found throughout the heart, it is most probable that if rheumatism be caused by a toxine, these changes arose concurrently in a general infection of its structures.

Allowance, must also probably be made for the influence of the surrounding tissue pressures. The pericardium, with a cavity between its two layers, and with numerous vessels and lymphatics lying in the deeper part of its visceral portion, will, in reacting to the rheumatic poison, permit free exudation into its sac, and after death the result is striking and at once appreciated. But in the ventricle wall the firm and contracting muscle will probably allow but little exudation, yet the morbid changes may in the gravity of their results be even greater. After death we may find little macroscopically, and when we do find changes we are naturally inclined to consider that they are less frequent in their occurrence, and commence after the onset of the pericarditis. We have many proofs that the morbid results produced by a poison may be extreme, yet the obvious morbid changes in the tissues themselves may be slight, as, for example, in acute osteomyelitis or in tetanus.

Another point is one upon which Dr. Lees has frequently laid stress, and to which he recently called attention when introducing the discussion upon rheumatic heart disease in childhood at the Edinburgh meeting in July 1898. It is that in rheumatism, dilatation is frequently very marked, yet the clinical symptoms, provided the patient be at rest, are often remarkably slight.

At first sight this is difficult to realise, but the explanation probably lies in the fact that, the function of the cardiac muscle is damaged in a peculiar way rather than destroyed by the rheumatic poison.

A tissue so complex as the cardiac muscle is liable to a variety of pathological changes, and these probably have a different morbid significance. Some of these changes may be far more detrimental to the vital properties of the muscle than others. Those that are the most destructive may cause death from syncope without appreciable dilatation, as occurred

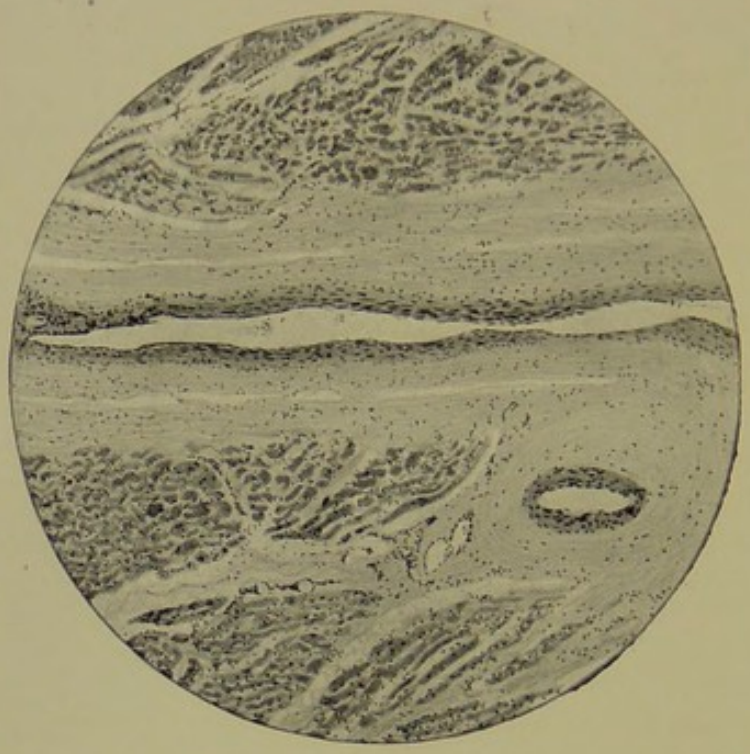


FIG. 6

Section of left ventricle from a case of recurrent rheumatism, showing extensive perivascular fibrosis.

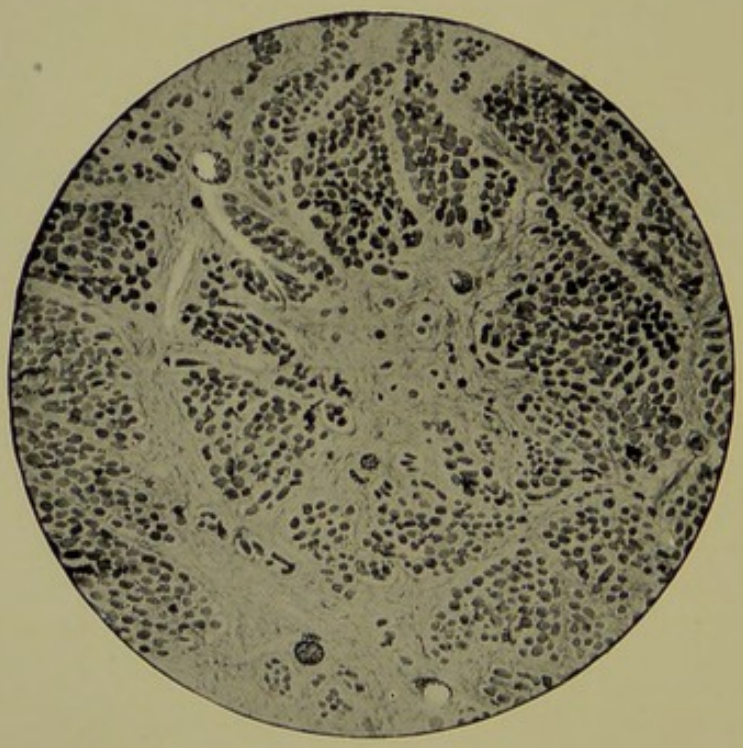


FIG. 7

Section from the left ventricle of a man aged 30, the victim of rheumatic fever in childhood, showing extensive fibrosis.

in the case of alcoholism referred to above, and also in the case of Addison's disease. Those changes which are less destructive may cause perversion or impairment of function, ending perhaps in death, but with great dilatation of the heart during life.

Clinically, the first definite evidence of advanced fatty degeneration of the heart may be sudden death ; and so we may expect that in rheumatism, with morbid changes of a less severe type, the symptoms due to the dilatation may be but slightly marked.

It is, also perhaps legitimate to consider what would have happened had the case recorded in this paper made a temporary recovery. The pericardium, we know, would have become less hyperæmic, have shrunk, and finally have become generally adherent. It is more difficult to follow the fate of the muscle, but probably much would have been replaced by fibrous tissue. The sections through the ventricle of the case of recurrent rheumatism support this view. If the boy had then died in a relapse, twelve months later, there would have been a temptation to lay much stress upon the mechanical effect of the obvious adherent pericardium, and little upon the loss of vital power due to the damaged muscle.

Finally, in rheumatic children it is certain that it is the active rheumatism that usually kills. It is very probable that in adults also active rheumatism is of more importance than might be thought ; and that the explanation of some cases of organic heart disease, which fail to react to treatment, and in which the symptoms far outweigh the clinical signs, is not the adherent pericardium so often found after death, but this active rheumatism injuring the cardiac muscle. The evidences of this rheumatism may be slight, and possibly we do not even yet fully recognise its manifestations. It is interesting that not infrequently there is in these unfavourable cases a history of recent rheumatism, and now and again such definite symptoms as arthritis develop during their stay in hospital. These symptoms could then hardly be due to a fresh infection, and are more probably an evidence of active rheumatism which had existed from the time that the cardiac breakdown brought them to the hospital.

Since this paper was communicated in February, microscopic sections of the cardiac muscle have been obtained in three

more cases, each of which show changes that bear upon the question considered in this paper. Dr. Cheadle, Dr. Lees, and Dr. Phillips have kindly given leave to give a brief outline of their histories.

Dr. Cheadle's case was that of a man of thirty, who had suffered from rheumatic fever in childhood, and was admitted for aortic and mitral incompetence. The symptoms were most urgent, quite overshadowing the physical signs. The sections of the left ventricle showed much fibrosis.

Dr. Lees' case, that of a girl of eighteen, was one of acute carditis, almost precisely similar to the case recorded, but even more convincing because there was no marked thickening of the pericardium. The fatty changes throughout the heart-wall were remarkable.

Dr. Phillips' case was that of a woman of twenty-three, who died of "infective endocarditis," probably of rheumatic origin. There were mural vegetations upon the endocardium of the left ventricle. The ventricle-wall showed *acute* inflammatory changes, but the pericardium was completely adherent from a previous rheumatic attack.

PAPER NO. III

A STUDY OF THE HEART-WALL IN DIPHTHERIA, RHEUMATIC FEVER, AND CHOREA

(Reprinted from the *Lancet*, May 12, 1900.)

The preceding papers having established the reality and importance of myocardial changes in rheumatism, in this one they are compared with those produced by undoubted infections, such as the diphtheritic and staphylococcic. The result is to strengthen the view that these myocardial changes in rheumatism are the result of an infective process. The changes described in the heart in the case of chorea provide a link in the chain of evidence establishing the rheumatic origin of this manifestation.

THE results which are produced in the heart by diphtheria and rheumatic fever respectively appear at first sight to be so different that to compare them might seem to be of doubtful value. Diphtheria recalls the sudden catstrophe of death from syncope and a heart the valves and pericardium of which are unaffected. Rheumatic fever, on the other hand, recalls a prolonged illness—a series of partial victories and defeats—associated pathologically with valvular and pericardial inflammation and clinically with valvular murmurs and pericardial friction sounds. Nevertheless, it is well known that diphtheria very frequently injures the heart in a way that differs from this dramatic nerve paralysis and syncope by acting as a direct poison to the cardiac muscle. The proof of this rests not only upon clinical and pathological evidence but upon the evidence of experimental pathology. Quite recently this action of the diphtheria toxins upon the heart has been emphasised by Dr. Villy, late assistant medical officer to the Park Fever Hospital, in a paper upon vomiting and cardiac failure in this disease.[1] There is in this form of cardiac affection dilatation of the heart (which is usually moderate), feebleness of the pulse, and disturbance of rhythm.

The first sound at the apex is short, and the pulmonary second sound becomes unduly loud; in severe cases the patient lies in bed pale and quiet with the muscle devoid of tone and the mind listless. The condition is one that may be seen early in the disease and may occur without any symptoms of nerve paralysis. In rheumatic fever, also, there may be dilatation of the heart which is sometimes considerable, and this may occur irrespectively of demonstrable valvular or pericardial inflammation. With this dilatation there are feebleness of the pulse, shortness of the first sound, and accentuation of the pulmonary second sound. There are also, to a minor degree, pallor, listlessness, and loss of muscular tone. The explanation of this condition in rheumatism is in all probability that the poison of the disease has also a direct effect upon the cardiac muscle.

In this paper evidence is brought forward in support of this view, and the argument is based upon the results of clinical observation and microscopical investigation of the heart-wall. These investigations, extending over three years, include observations upon 18 cases of rheumatic heart disease, four cases of diphtheria, a case of chorea, and a case of septicæmia in an animal injected with a pure culture of staphylococci. One of the cases of diphtheria, one of the cases of rheumatism, and the case of chorea are selected from these to illustrate the salient points in this argument. For the sake of clearness a brief allusion will first be made to the clinical course of the cases of diphtheria and rheumatism. The details of the microscopy are dealt with at greater length and the extreme changes in the heart-wall in these two examples are represented in the drawings from the sections of the myocardium.

Case 1. *The case of diphtheria.* The patient, a child, about five years of age, contracted a sore-throat which developed the characters of faucial diphtheria. Later in the illness signs of progressive and grave cardiac failure became evident. The pulse was extremely feeble and there were pallor, vomiting, restlessness, and finally almost complete suppression of urine. There was no evidence of diphtheritic neuritis, and the child died from cardiac failure on the seventeenth day of the illness.

Dr. John Morton made a necropsy within 24 hours of death and brought us for examination parts of the left ventricle and

kidneys. The kidneys showed extreme congestion but no indication of an acute nephritis. The condition of the myocardium was as follows: The Macroscopic changes. The cardiac muscle was pale and the pericardium was normal. The Microscopic changes. Fixative Hermann's fluid. Stain safranin.

1. *In the muscle fibres.* Transverse striation was lost in many places, but was still present in others. In some fibres longitudinal striation was more evident than usual. The contour of many of the fibres was irregular and the irregularity was due in part to shrinking in width from destruction, and in part to bulging from fatty changes. Some of the fat droplets were of considerable size, and the areas in which the fatty changes in the fibres were marked were, as is usual in diphtheria, very irregular in distribution. Some of the fibres were completely destroyed and the field of section had in these places a reticular structure. Transverse sections of the muscle fibre showed the variability in their size with great distinctness.

2. *In the nuclei.* The nuclei of the muscle fibres showed great variability in size and staining properties. In some fibres the nuclei were swollen, in many divided into two, and in some of these a few dark granules could be seen between the two nuclei. Some of the swollen nuclei stained diffusely and exemplified very clearly the condition of hyperchromatosis. The granules that were present in the space between the divided nuclei stained with the methyl green, and did not, as is the rule in more chronic affections of the heart, show that dark-brown colouration which is so characteristic an appearance in this tissue. Other nuclei were very small and also stained a diffuse green. Some were round in outline and appeared as mere dots in the centre of the fibre. In some the chromatin network was definite and evenly distributed; in others it was massed to the poles, leaving a colourless centre; and in others it was centric, leaving a colourless periphery. In many cases the protoplasm of the muscle fibre in the neighbourhood of the nuclei showed an appearance of vacuolisation.

3. *In the interstitial tissue.* Some portions of the left ventricle were fixed in perchloride of mercury and the sections showed that there was no increase in the fibrous tissue of the ventricle wall, but in places there was an increase in the cellular elements between the fibres.

4. *In the pericardium.* The pericardium was not inflamed.

There was, then, in this case a severe destructive lesion of the essential elements of the heart-wall, such as has been recorded by many other observers in this form of diphtheritic heart failure.

At this point it is necessary to make a brief allusion to the microscopic investigations of the heart-wall in animals that have been injected with diphtheria toxins. This work has been carried out by various experimental pathologists and an allusion must be made to a paper by Mollet and Regaud upon the subject.[2] These observers found that lesions of the muscular fibres were constant and that they occurred sometimes alone and sometimes together with an interstitial leucocytosis. Vascular lesions in the myocardium also were frequent. Macroscopically there were in some cases endocardial, myocardial, and pericardial hæmorrhages, and an abnormal appearance of the myocardium was frequent. (1) In the muscle fibre under the microscope. There were granular and fatty changes in the muscle fibres and sometimes vacuolisation. Striation was often lost. (2) In the nuclei. The nuclei were found distorted, swollen, and stained with difficulty. (3) In the interstitial tissues. There was in some cases an increase of the cellular elements between the fibres. More details were given in this paper as to the date of appearance and probable meaning of these abnormalities, but it is sufficient for the present purpose to recognise the similarity of these changes to those described in the case of diphtheria.

Case 2. *The case of rheumatism.* A young man, aged 19 years, was admitted into St. Mary's Hospital on December 4, 1899, for pains in the limbs and morbus cordis. There was a history of three previous attacks of rheumatic fever, the first occurring at the age of seven years. When admitted the patient was very ill, the face was cyanosed, and there was orthopnœa. The temperature was 102° F., the pulse was 108, and the respirations were 40. The pulse was feeble and the heart was excited and greatly dilated. There was some chronic mitral disease. Pleural friction was audible on both side, but we did not detect pericardial friction at the time of his admission. The next day there was general pericardial friction, and death rapidly followed on the 7th.

The necropsy was made 14 hours after death and some

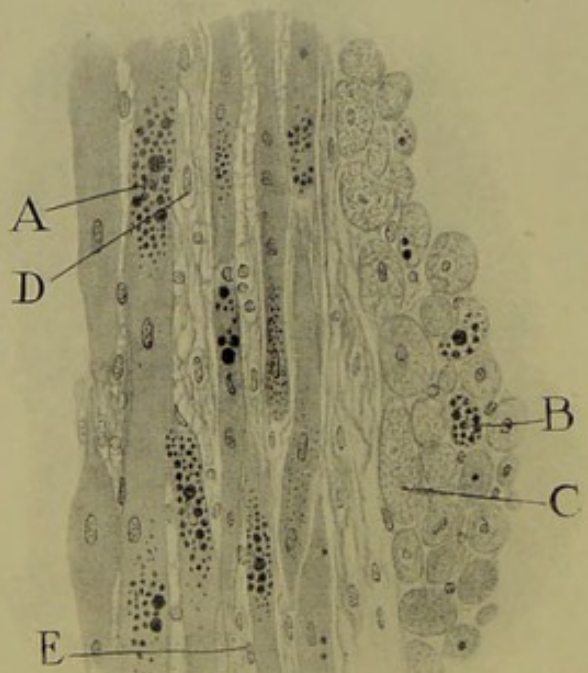


FIG. 8

Section of the left ventricle from a case of diphtheria.

A. Muscle-fibre showing localised fatty change.
B. Fatty change in transverse section of muscle-fibre.
C. Destruction of the myoplasm.
D. The same in longitudinal section.
E. Cellular elements between the muscle-fibres.

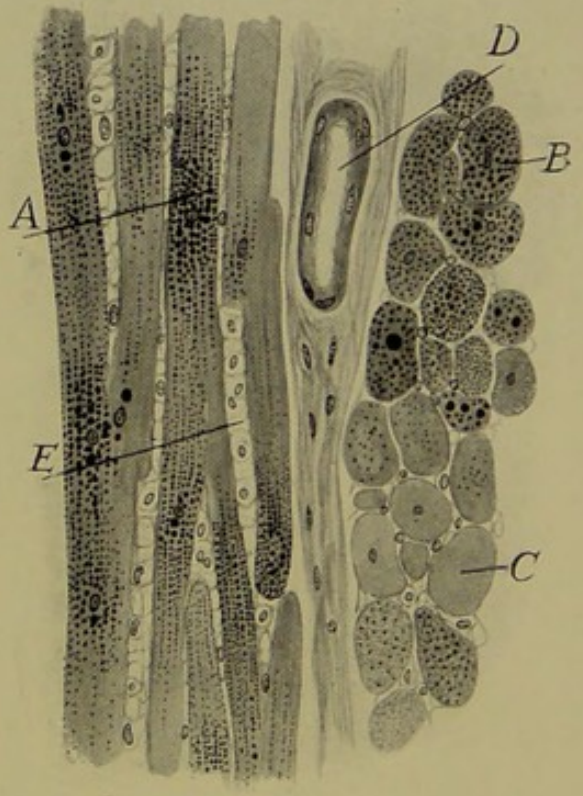


FIG. 9

Section of left ventricle from a case of acute rheumatic carditis.

A. Fatty change in the muscle-fibre.
B. The same in transverse section.
C. Normal muscle-fibre. *D*. Capillary blood-vessel.
E. Distended capillary between muscle-fibres.

ounces of slightly turbid fluid were found in the pericardial sac, with some recent lymph especially upon the posterior aspect of the heart. There was no great distension of the pericardial sac with this fluid and by no means sufficient to account for the wide cardiac area during life. The appearance of the heart-wall was remarkable for its great pallor. The mitral valve showed no recent changes but those of a moderate stenosis due to previous fibrosis. The aortic valve showed recent vegetations springing from previously uninjured cusps. The valves on the right side were unaffected.

In the muscle fibres under the microscope. The striking feature was the extreme fatty change, some of these being almost a mass of fine fat droplets. This change extended through the ventricle wall and was remarkably general. In some cases, nevertheless, a considerable number of fibres had escaped that change and showed distinct striation. The contour of the fibres was preserved and that extent of destruction seen in the case of diphtheria was absent.

Under higher magnification. Stained by methyl green. The nuclei showed well and their size was fairly constant. Marked alteration of shape and staining properties were not as evident as in the case of diphtheria. Under this high magnification minute clear spaces could be seen in the muscular fibres in addition to the fatty change.

There was some cell exudation between the muscle fibres in the neighbourhood of the vessels lying in the interstitial tissue.

The pericardium showed recent inflammatory change, the endothelial lining still remaining intact. There was no evidence of a previous pericarditis.

To summarise : there was disease of the muscular fibres, but the destructive nature of the change was not of the same gravity as in the case of diphtheria, and it is probable that these changes were due to the direct action of the rheumatic poison upon the myocardium. At this point a difficulty arises, for in rheumatism as yet no specific organism has been generally admitted and no toxins can be measured out by pathologists for inoculation experiments upon animals. There are no investigations to be put side by side with those of Mollet and Regaud to which reference has been made and to argue that because the changes found in the heart-wall in rheumatism and diphtheria are very similar it follows that they are neces-

sarily due to a direct action of their poisons may seem hazardous since rheumatism and diphtheria are widely different diseases.

Between rheumatism and septic infections there is a closer link, and a brief reference is now made to an investigation of the cardiac wall from a rabbit that had died from septicæmia caused by an inoculation of a pure culture of staphylococci. The animal died on the sixth day after the injection of staphylococci. The kidneys were full of small pyæmic abscesses, and in the heart-wall between the muscle fibres were foci of inflammatory exudation containing staphylococci. The cardiac muscle showed definite fatty change, patchy in distribution. In a paper upon venous thrombosis in rheumatic fever (1898) [3] and in papers read before the Royal Medical and Chirurgical Society and at the Portsmouth meeting of the British Medical Association [4] in 1899, allusion was made to similar inflammatory foci in rheumatic fever. The close relation that rheumatism bears to septic infections is undoubted, and this observation is of value because it is an evidence that fatty changes in the heart muscle are not necessarily the result of prolonged impairment of the cardiac circulation. It is of interest, also, because it appears to throw some light upon the morbid anatomy of the third case—the case of chorea.

Case 3. *The case of chorea.* This case was an example of that type of chorea in which the movements are extremely violent, and death is not associated with gross cardiac inflammation. The heart after death showed only a slight inflammation of the mitral valve. Microscopical investigation showed numerous micro-organisms in the valve and in the vessels at the base of the valve. Many sections of the left ventricle were examined and some distinct foci of inflammatory exudation were found comparable to those which may be found in acute rheumatism or more obviously in the acute pyæmia from the injection of staphylococci into the circulation. In addition there was early fatty change in some of the muscle fibres, patchy in distribution. The close resemblance between this condition and that found in the rabbit's heart is suggestive, and both appear to us to strengthen the probability that rheumatism directly injures the cardiac wall.

To return once more to the case of rheumatic fever. A brief analysis of this case furnishes additional evidence in

favour of the myocardial change being due to the direct action of the poison upon the muscle. The importance of the case lies especially in the fact that the pericarditis was a terminal event in the disease, and that the pericardium had not been attacked in the previous rheumatic outbreaks. When the patient was first admitted there was no pericardial friction, though the illness had extended over at least four weeks and the heart was greatly dilated. This absence of pericardial friction was no complete proof of the absence of pericarditis, but after death recent flakes of lymph and a considerable quantity of slightly turbid fluid were found in the pericardial sac—a sure indication of an acute rheumatic inflammation of brief duration. If, then, the clinical and pathological facts are coupled together there can be no doubt that in this case the pericarditis was a terminal event. The extreme myocardial disease cannot, therefore, be explained as secondary to pericarditis, and no one would maintain that it was the result of a comparatively slight valvular lesion. It is most probably to be explained as the direct effect of the rheumatic poison. This view is also supported by the finding of similar myocardial disease in four other acute cases of rheumatic fever, two of which have already been published.[5]

The practical bearing of this view is very considerable. It emphasises the important part that active rheumatism takes in the history of rheumatic morbus cordis. It is realised that in children active rheumatism is of vital importance, a fact further borne out by the analysis of fatal cases of rheumatic fever in children under 12 years of age.[6] In adults the occurrence is more liable to be overlooked. The condition of chronic rheumatic morbus cordis with the secondary changes that result from previous valvular inflammation is apt to be raised to the position of a primary disease rather than to be classed as a symptomatic affection and the breakdown to be sought for in mechanical overstrain. Yet in adults, as in children, fleeting rheumatic pains in the joints and pleuritic and præcordial pains are all frequent at the time when the heart gives way. It may be safely asserted that if a children's hospital is full of cases of active rheumatism and chorea an adult hospital will be full of broken-down chronic heart disease of rheumatic origin. After death in these chronic cases recent granulations may be found on the valves without any clinical

evidence of rheumatism to lead to a suspicion of the active process—a point to which Dr. A. Garrod has also called especial attention at the recent discussion on rheumatism at the Chelsea Clinical Society. It is difficult in these complex cases to point with certainty to myocardial failure as the cause of the cardiac breakdown ; for there is no myocardial friction sound or bruit to clinch the diagnosis. The results have to be judged often enough by symptoms which may be almost as well explained on the hypothesis of a mechanical failure. Yet the point is one of importance, for if due to rheumatic affection of the myocardium the power of the heart is undermined at its very foundation.

Another practical point, perhaps the most important of all, concerns the first attacks of rheumatism that are met with most frequently in childhood. The myocardium may show signs of the rheumatic disease before the valves or pericardium,[7] and no clinical fact is more striking than the unobtrusive method in which rheumatism produces in childhood heart disease which is often incurable. In such cases as these, to wait for a definite systolic valvular murmur before deciding that the heart is affected is dangerously akin to awaiting fæcal vomiting for a proof of intestinal obstruction. If the development of incurable rheumatic heart disease is to be satisfactorily arrested the best opportunity will be before definite proof of its existence is demonstrable by a valvular murmur.

A study of the microscopical details of the myocardial changes in diphtheria and rheumatism explains possibly the clinical fact that the dilatation in diphtheria is usually not so marked as in rheumatism, but the tendency to a fatal termination is vastly greater. The poison of diphtheria appears to destroy the muscle fibres far more than does that of rheumatism. The drawings in this paper, made under a comparatively low power, are sufficient to illustrate this point. This is, a warning not to raise dilatation of the heart—a clinical entity so definite and well recognised—into the position of a primary disease, for if this be done it is natural enough to consider that the greater the dilatation the greater the danger. Yet the truth of this, even for any one disease, is only approximate, for all diseases vary in their virulence and individual effects, and those that attack the cardiac wall may damage the

muscle fibre at one time far more than at another. A poison acting upon the myocardium with great virulence will, it is clear, cause such an impairment of the heart's force that death must occur before there is marked dilatation, an occurrence not infrequent in diphtheria. It is probable that in rheumatism also this question of greater or less virulence is an important one. Though the extent of the cardiac dilatation must necessarily be a sign of very great significance, it is in these myocardial affections that the paramount importance of the symptoms becomes apparent ; for these symptoms, we should suppose, even more than the dilatation, are an index of the muscle failure. In this principle probably lies the explanation of some of those more obscure cases of cardiac rheumatism, cases in which, without evidence of valvular or pericardial disease, there remain unaccountable breathlessness, præcordial pain, and other indications of cardiac inadequacy. Finally, from the theoretical standpoint the changes in the cardiac wall in acute rheumatism are of interest because their nature and complexity are decided evidence in favour of rheumatic fever being due to a microbic infection. In this paper it may be pointed out that the view that the poison of rheumatism acts directly upon the muscle does not imply that this poison is necessarily the result of a microbic infection, though, short of absolute proof, the infectious origin of rheumatic fever appears to rest upon very strong evidence.

In conclusion, our thanks are again due to Mr. H. G. Plimmer, pathologist to the hospital, for invaluable advice as to technique and methods of investigation whilst working in the laboratory at St. Mary's Hospital.

REFERENCES

[1] "Vomiting and Cardiac Failure in Connection with Diphtheria, *Medical Chronicle*, September 1899.

[2] "Myocardite Diphthérique," *Annales de l'Institut Pasteur*, No. 2, 25 Fevrier 1897.

[3] "Three Cases of Extensive Venous Thrombosis associated with Severe Rheumatic Carditis," the *Lancet*, July 23, 1898, p. 206. Paper No. VI.

[4] "Rheumatic Pericarditis, with an Investigation into the Microscopy of Rheumatic Morbus Cordis, *Transactions of the Royal Medical and Chirurgical Society*, 1899. "Some Observations upon the Pathology of the Myocardium," *Brit. Med. Jour.*, November 1899. Papers Nos. II and IV.

[5] "A Case of Virulent Acute Rheumatism with Extensive Purpura," the *Lancet*, October 28, 1899, p. 1163. Paper No. VII.

[6] Lees and Poynton, "An Analysis of 150 Fatal Cases of Rheumatism in Children under 12 Years of Age," *Transactions of the Royal Medical and Chirurgical Society*, 1898. Paper No. I.

[7] Lees and Poynton, "Acute Dilatation of the Heart in the Chorea and Rheumatism of Childhood," *Transactions of the Royal Medical and Chirurgical Society*, 1888. Paper No. I.

PAPER NO. IV

OBSERVATIONS UPON THE PATHOLOGY OF THE MYOCARDIUM

(Reprinted from the *British Medical Journal*, November 4, 1899.)

This paper, while to some extent a review of the preceding observations, was written with the view of emphasising the important bearing that an intimate study of myocardial changes in infective diseases has upon the clinical study of organic heart disease. Although it is but an insignificant contribution in itself, we have included it here to illustrate that our constant endeavour has been to apply the results of experimental and laboratory observation to the problems of practical medicine.

This subject is one that has naturally attracted the attention of many observers, and is in danger of being considered already too well worn. It seems, however, possible that a systematic examination of the myocardium in various conditions may prove of great value in the study of cardiac diseases. This is the more probable because pathology affords a continual assistance both by the improvements in its methods and the new light that bacteriology throws upon even well-established facts. In the clinical study of heart disease the detection of a valvular murmur or pericardial friction sound is among the surest evidences of organic heart disease, and the endocardium and pericardium accordingly take a most prominent position in the clinical history. To the morbid anatomy of the heart much the same applies, for the evidences of endocarditis or pericarditis, recent or of old standing, are more easily recognised than are similar changes in the cardiac wall itself. Possibly then it may be that over much has been attributed to the damage of these structures, with the result that the myocardium has been regarded rather as a passive structure than an active muscular wall, and that mechanical explanations have taken too great a part in the

interpretation of the morbid results that are presented. In view of this possibility it is a suggestive statement—the outcome of experience—that in judging of the gravity of a case of organic heart disease the symptoms are of more import than the physical signs, for the symptoms are mostly determined by the failure of the circulation due to the enfeeblement of the heart-wall, whereas the physical signs are determined mostly by the nature and extent of the valvular lesion. It is suggestive also that in chronic heart disease of rheumatic origin, when failure of compensation occurs, there is not as a rule a history of mechanical overstrain, but frequently in adults and almost invariably in childhood, a history of a relapse of rheumatism.

The widest field for investigations upon the myocardium is provided by rheumatic fever, because of its frequent occurrence, and because, though it varies much in its severity, it usually gives rise to considerable resistance within the body. This resistance is apparent in the inflammation, fibrinous exudation, and fibrosis that result from its invasion.

Since these phenomena of inflammation take place in the neighbourhood of the vessels, and must be to some extent modified by the mechanical surroundings, the arrangement of the coronary circulation within the heart becomes a question of some interest. If a section is made transversely across the base of the heart through the valve rings, numerous vessels can be seen arranged in an areolar tissue beneath the endocardium around the orifices. A vertical section through the mitral valve and auriculo-ventricular junctions of a heart injected with Prussian blue, shows these vessels lying in the connective tissue at the base of the valve, and in the valve itself lacunæ are also visible. A similar section through an inflamed valve shows a considerable exudation in the areolar tissue at the base of the valve in the region of these vessels. In the acute and severe cases of rheumatic fever this cellular exudation can be traced around the vessels beneath the endocardium of the auricle and ventricle, but may give rise to no visible sign upon the surface of the endocardium. If, however, the leucocytic infiltration invades the endocardium from beneath, as it may invade the valve from its base, then yellow points can be detected upon the surface. The pericardium when inflamed shows similar changes even more

definitely, for there is a free surface toward the pericardial cavity, and the deep part of the visceral layer contains numerous vessels. Should the inflammation be subacute, the development of fibroblasts and the earlier stages of formation of an adherent pericardium can be readily traced. A study of the arrangement of the vessels around the mitral orifice, by vertical and transverse sections in healthy and diseased conditions, coupled with a study of the changes in an inflamed pericardium, gives perhaps the most realistic picture possible of the development of mitral stenosis as an after-result of rheumatism.

In the wall of the heart the capillaries are seen to run between the several muscular fibres, and are encompassed by muscular walls. In the intermuscular septa there is some areolar tissue, and in at any rate some cases of rheumatic heart disease cellular exudation can be traced at these points spreading through the heart wall in scattered foci. These foci have been found in a case where pericarditis was only manifested the day before death, and also in cases of recurrent rheumatism where the pericardium was adherent, and not in a condition of acute inflammation. In some cases of recurrent rheumatism, also, there is an increase in the interstitial tissues of the heart wall: a fibrosis spreading from the vessels, and implicating the adjacent muscular bundles, analogous to the fibrosis of the valves or pericardium. The question arises, whether these changes in the heart wall itself, are secondary to a pericarditis, coincident or even independent of that? At first sight, perhaps, this may seem a point of small importance, but from the clinical aspect it is a question of great interest. If the myocardial inflammation is secondary to pericarditis, then the occurrence of pericarditis is doubly grave by reason of the injury to the pericardium itself and to the heart wall also. But if the myocardial changes may arise independently, then it is possible that many cases of acute rheumatism in which there is no pericarditis may cripple the heart in this insidious way, especially if the pericardium is already adherent. One case is of value in this connection. The patient, a young woman, died in the third attack of rheumatism. There was mitral valvulitis and great dilatation, but macroscopically no pericarditis. Upon microscopic examination there was evidence of myocarditis, and pericarditis was just commencing. Other observers have only found

changes in the superficial layers of the heart wall immediately beneath the inflamed pericardium, and the recent researches of Professor Hill and Mr. Barnard have increased our knowledge of the function of the pericardium as a support to the heart wall; also, too, these observations have been utilised by Dr. Sequeira in a paper recently read before the Royal Medical and Chirurgical Society to explain the grave importance of pericarditis as a cause of cardiac dilatation. Nevertheless, there is much in favour of the view that myocardial changes are not necessarily dependent upon pericarditis; and though the pericardium may have an important function in checking dilatation, that dilatation, and marked dilatation, too, may occur without any weakening of the pericardium by pericarditis.

The condition of the cardiac muscle in rheumatic fever is the next point that claims attention, and is a question surrounded with difficulties. It may be generally asserted that the more specialised a tissue the more difficult it is to feel sure of the existence of morbid changes in its structure, and of their proper interpretation. This is a difficulty, too, which is enhanced by the post-mortem changes that occur in the tissues. Nevertheless, whatever view be taken of the actual cause of rheumatism, it is generally allowed that there is an alteration in the blood state, and this raises the possibility of the cardiac muscle suffering as a consequence. Moreover, there is considerable evidence in favour of this view. In some rare cases of rheumatism death has occurred from cardiac failure with dilatation, and no pericarditis has been found after death. Recently in two acute cases of rheumatism with pericarditis general fatty changes were found throughout the heart, including the papillary muscles. Though this is not conclusive—for it may be possibly objected that this change is not a primary one, but secondary to the enfeebled circulation—nevertheless, it points, strongly to some profound injury to the cardiac muscle, which has resulted in this circulatory failure. In a question of this kind the complexity of the chemical processes within the body requires to be remembered, and it is very possible that the particular condition which is recognised by certain comparatively rough staining methods as a fatty change may be the end result of widely different antecedent chemical processes. There are other alterations,

too, in the cardiac muscle in acute rheumatism beside these fatty changes, such as hyaline degeneration, loss of striation, and vacuolisation. Even in children granules sometimes staining with thionin can be detected in the region of the nucleus, and the nucleus itself may also show numerous granules. This brief allusion to the alterations in the cardiac muscle is made rather with the object of showing that caution is required before pronouncing that the muscle is not affected in rheumatism, than with the intention of stating that it is invariably affected. Far more numerous observations are required to settle such a point, and experimental pathology must be requisitioned before the true value can be attached to these more obscure morbid changes in the muscle. The implication of the cardiac nerves is another important question.

There is one other condition somewhat rare in its occurrence but of deep clinical interest in which the myocardium may show much disease. During life the symptoms are those of breathlessness, angina, and a tendency to syncope. The end is usually quite sudden, and the necropsy shows as the most striking feature an acute inflammation of the aorta. Two such cases we examined and published fully in the *Lancet* in May 1899 illustrated this. It was evident that in these cases analogous changes were proceeding in the heart and arterial wall.

In conclusion an endeavour has been made in this paper to support the view that a systematic investigation of the cardiac muscle may prove of some practical value in the study of cardiac diseases, especially if the clinical facts can be at the same time recorded.

PAPER NO. V

THREE FATAL CASES OF EXTENSIVE VENOUS THROMBOSIS ASSOCIATED WITH SEVERE RHEUMATIC CARDITIS

(Reprinted from the *Lancet*, July 23, 1898.)

The three cases recorded here are, we believe, of sufficient rarity to be of interest in themselves. The pathological investigations bring additional support to the contention that the rheumatic processes within the body are the result of some infective process.

THE first case, that of a girl aged nineteen years, was admitted into St. Mary's Hospital, under the care of Dr. D. B. Lees, for shortness of breath and swelling of the arms and legs. In January 1897, she had suffered from a very severe attack of rheumatic fever for which she had been kept in bed for thirteen weeks and during this time she was reported to have had both pneumonia and peritonitis. The history of this present illness dated from August 1897, when the patient noticed swelling of the legs and abdomen; in September, however, there was decided improvement. In the first week in October the symptoms again became more urgent and a few days before admission to hospital the left arm suddenly commenced to swell. On admission, on October 19, her condition was extremely grave. She was very pale and distressed. The conjunctivæ were icteric and there was orthopnœa. The temperature was subnormal and remained so throughout the illness. The legs and thighs were œdematous. The left arm and hand were much swollen and the face was puffy; the right upper extremity pitted on pressure and the upper part of the chest was œdematous. The cardiac condition was that of advanced organic disease. The pulse was 90 and very irregular in force and frequency. Not all the beats of the

heart were perceptible at the wrist. The impulse was diffuse and the heart was much and generally dilated. A systolic apical murmur was heard and an accentuated pulmonary second sound. The air entry and percussion note were impaired at both bases posteriorly. The liver was large and tender and the urine contained some albumin and was loaded with urates. For the next few days there was some slight improvement, but at midnight on October 31, the patient became aphasic, the right hand appeared to be weak, and the right leg was kept semi-flexed. Deviation of the head and eyes did not occur. She appeared to understand what was said, but gradually became more and more drowsy. Then followed loss of sphincter control, difficulty in swallowing, coma, and finally death.

A post-mortem examination was made twenty-four hours after death. The pericardium was found totally adherent, in places firmly and in other parts only feebly so. Both auricular appendices were compressed by the pericardium and round the large vessels the pericardial and mediastinal tissues were œdematous. The heart weighed 16 oz. and the cavities were dilated, especially that of the right ventricle. The mitral orifice was slightly narrowed by old rheumatic endocarditis, but the deformity of the valve was moderate. The aortic valve was incompetent from previous rheumatic endocarditis. The tricuspid valve was incompetent but there were no rheumatic changes in this valve. The pulmonary valve was natural. The right auricle was empty. The left ventricle was 1¼ in. thick. The muscle was firm and of good colour. Both lungs were adherent to the chest wall. Both internal jugular veins were like firm cords and contained adherent clot throughout their entire extent. The lower end of the left internal jugular was white and narrowed and very firm. Both venæ innominatæ contained adherent clot and the left one could hardly be recognised amongst the œdematous tissue of the mediastinum. The upper part of the superior vena cava contained clot which was firmly adherent to one side of the wall of the vein but did not occlude the entire lumen or project into the auricle. There was no clot in the inferior vena cava. The brain was generally softened but no change was found locally or in any particular vessels. The liver showed advanced chronic congestion due to tricuspid

incompetence. The kidneys were indurated from chronic venous congestion.

The second patient a young woman, aged twenty-one years was admitted to the hospital under the care of Dr. Cheadle on February 9, 1898. When a child she had suffered from an attack of scarlet fever which was followed shortly afterwards by an attack of rheumatic fever. Two years before the present illness she suffered from a second attack of rheumatic fever. The final illness began gradually with weakness, increasing dyspnœa and œdema of the face and legs. On admission to hospital the patient was very ill, the face was puffy, and she was very anæmic. The temperature was 101° F., the pulse averaged 128 and the respirations 28. The legs pitted on pressure. The pulse was regular and of low tension; the heart was dilated. On auscultation a loud systolic murmur was heard all over the front and back of the chest; the impulse was diffuse and a systolic thrill could be felt. Bronchitic sounds were heard over both lungs. Neither the liver nor the spleen could be felt below the costal arch. The urine contained albumin, blood and some tube casts, and the specific gravity was 1020. During the next week there was marked dilatation of the heart, with irregular pyrexia, free sweating, and decided increase in the œdema and dyspnœa. On February 18, the liver and spleen could both be felt below the costal margin. The urine was scanty and contained albumin and blood, but no more casts were found in spite of repeated and careful search. One special feature of this case was a frequent and harassing cough, for which there was no apparent explanation. On the 21st there was complaint of pain in the wrists and left forearm, the face was more puffy and the conjunctivæ were icteric; the pain in the forearm was localised to the inner side over the region of the flexor carpi ulnaris and palmaris longus; this area was very tender, but there was no local redness. During the next week there was distinct improvement and the heart became smaller, but this was not maintained and in the first fortnight of March the pyrexia, which had been persistent, became more marked and more irregular. The pulse was now irregular and there was orthopnœa, with attacks of severe dyspnœa. On March 17, sudden pain was felt in the left loin and more blood appeared in the urine. The left lung was dull at the base and over a con-

siderable area tubular breathing was heard. The face, which had become almost free from œdema, now again became puffy, especially upon the left side. On the 19th some casts were again found in the urine together with blood, the heart was very dilated, and the patient was moribund. She died on March 20.

At the post-mortem examination which was made on March 21, the pericardium contained a slight excess of clear fluid, but there was no definite pericarditis. The heart weighed 14 oz. All the cavities were much dilated ; in addition there was distinct hypertrophy of both ventricles and of the left auricle. The muscle was pale. The mitral orifice was slightly larger than natural, as also was the tricuspid. There were numerous exuberant granulations on the mitral valve and a portion of the anterior cusp was free, the chordæ tendineæ attaching it to the papillary muscle having ulcerated and given way. Vegetations had also spread along the anterior wall of the left auricle upon the inner surface. On the wall of the left ventricle below the mitral valve were a few isolated vegetations. The tricuspid, aortic, and pulmonary valves were not affected. The lower lobe of the left lung was solid with pneumonic change ; the right lower lobe was extremely congested but did not sink in water. The spleen weighed 8 oz. and there were two infarcts within it, one of which was quite recent. The liver weighed 44 oz. and was fatty. Each kidney weighed 6 oz. and contained one infarct ; the capsule of each was thickened but not adherent ; the cortex was pale. In the left internal jugular vein was a clot extending from the junction with the left subclavian to the angle of the jaw. This was pale and adherent to the wall, especially in the lower part, where the vein was cord-like. The innominate veins and right jugular, and the inferior vena cava and its larger tributaries were not affected. The brain appeared to be quite natural.

The microscopical examination was undertaken with the assistance of Mr. Brincker. The pericardium showed in the visceral layer some early inflammation. The heart muscle had lost much of its striation and most of the fibres showed pigmented perinuclear granules. The mitral valve was much affected by inflammation, but no micro-organisms were demonstrated in the granulations. Sections

of the left internal jugular vein showed an organising thrombus, but micro-organisms could not be demonstrated in the vein wall, which was not distinctly thickened. No organisms were found in the clot. Sections of the right internal jugular, appeared to be natural. The left lung was pneumonic and numerous diplococci were demonstrated by Gram's method. The kidneys showed no sign of interstitial inflammation from any old-standing nephritis. In the neighbourhood of the infarcts there were hæmorrhages in the substance, and the renal epithelium showed much cloudy swelling, but otherwise nothing remarkable was observed.

A third case, that of a girl aged nine years, was admitted to the hospital under the care of Dr. Cheadle on February 19, 1898, for swelling of the body and limbs and collapse. Two years previously she had suffered from an attack of scarlet fever, since which time the heart had been affected. There was a marked rheumatic history upon the father's side. The mother unfortunately was addicted to alcoholism, so that it was not possible to obtain a careful description of the onset of the present illness. The child had been ailing for three weeks with pain in the chest and cough, and during the last week dropsy was noticed. On admission to hospital the patient was very pale and the face was œdematous, the expression being distressed. There were slight cyanosis and orthopnœa. The temperature was 97.4° F., the pulse averaged 100, and the respirations 30. The fingers were clubbed, the lower extremities were œdematous, and the front of the chest pitted on pressure. The abdomen contained some fluid. The pulse was irregular, weak and small. The heart was much enlarged; the left limit was four finger-breadths external to the left nipple and the right limit was three finger-breadths external to the right margin of the sternum. There were marked epigastric pulsation, præcordial bulging, and a systolic and diastolic thrill. At the apex a systolic murmur was heard and over the aortic cartilage systolic and diastolic murmurs were audible. There was also a doubtful pericardial scratching sound heard to the left of the sternum. The air entry was impaired over the bases of both lungs and there were scattered rhonchi and sibili over both the front and the back of the chest. The appetite was good, though the tongue was furred. The urine was acid, the specific gravity being

1025; it contained albumin and blood, but no casts. The liver was enlarged and pulsating. The child slept with her face turned towards the pillow. After admission to hospital the œdema gradually subsided and the blood in the urine disappeared. Steady improvement was maintained until March 10, when pleural friction was heard in the left axilla and there was distinct dullness on percussion at the left base. The urine contained a trace of blood, but there was not any rise of temperature. After this outbreak there was again improvement, the œdema disappeared, the liver became smaller, and the signs in the left pleural cavity cleared up. On April 10, there was once more pain in the left side and also dullness at both bases. The axillary glands were noticed to be enlarged. The heart was more dilated and the action was feebler; the liver also had increased in size. On the 13th the left side of the face became swollen and on the 16th there was marked œdema of the right side of the neck, the face was purple, and the eyelids and lips were swollen. Both sides of the neck were tense, and tender on the least pressure. Movement of the neck was painful. The temperature was subnormal; there was no swelling of the legs or ascites. Dr. Cheadle saw the child and diagnosed thrombosis of the internal jugular veins. On the 17th the right arm began to swell. Shortly after the right arm had become swollen the left arm began to swell. The chest was œdematous. The child was very apathetic and took food badly. On the 18th she was very drowsy and apathetic and the face was cyanosed. At midday there was sudden dyspnœa and two attacks of great restlessness occurred. The extremities became cold and the pulse at the wrist was imperceptible; there was much suffering. On the 19th the œdema of the right arm was extreme and there was tenderness on pressure, but the face was less swollen. The respiration was slow and sighing. On the 20th two firm cords were felt in the lower part of the neck. The legs and feet were a little swollen. The area of cardiac dullness was now enormous and there was loud general pericardial friction. Sharp crepitations were heard over both lungs. The urine was scanty; it contained a trace of albumin and no blood. Food was refused and death took place on the 21st.

A post-mortem examination was made on February 22. The cranial cavity was not opened. The pericardium contained

between 4 oz. and 5 oz. of turbid fluid and the surfaces were coated with recent lymph. All the cavities of the heart were dilated. Both ventricles were hypertrophied, the right proportionately more than the left. The mitral orifice was incompetent, the valve segments and chordæ tendineæ were thickened, and in addition along the cusps were some recent vegetations. The tricuspid orifice was incompetent and along the cusps were recent vegetations. The auricles were dilated, but the right auricle was empty. The aortic valves were thickened and incompetent and beaded with recent vegetations. The pulmonary valves were natural. The following veins were occluded by thrombus : the right innominate, subclavian, axillary, internal and external jugulars—the last only in the lower part of its course ; the left internal jugular, external jugular, inferior thyroid, axillary, subclavian and innominate. In its upper two-thirds the superior vena cava was occluded. Looking into it from the auricle a pale, soft clot could be seen, not adherent, blocking completely the lumen of the vessel ; higher up the clot was quite firm. Both internal jugulars felt like firm cords in their lower part and were white and small, whereas in the upper part they were bulged with soft clot. The left innominate was small and white and only admitted a small probe. The veins were more adherent to the surrounding tissues than usual. Though more extensive it is quite comparable to the condition found in Case 1, but there was no pericardial adhesion or obliteration of auricular appendices as in the latter. The inferior vena cava and its tributaries were natural. Unfortunately, whether as in the first case the brain was œdematous or whether the lateral sinuses were occluded could not be ascertained. It is, however, certain that the clotting did not begin in these sinuses, for the further the distance from them the older was the thrombosis in the jugular veins. Nodules were present on the dorsum of the right foot and in the scalp. The remaining organs showed the usual secondary changes from advanced morbus cordis. There was no evidence of infarction.

Cultivations from the pericardial fluid, lymph, and blood-clot were negative, as also were films made from the pericardial fluid and blood-clot. The conditions of the heart wall and pericardium are of interest because they represented the

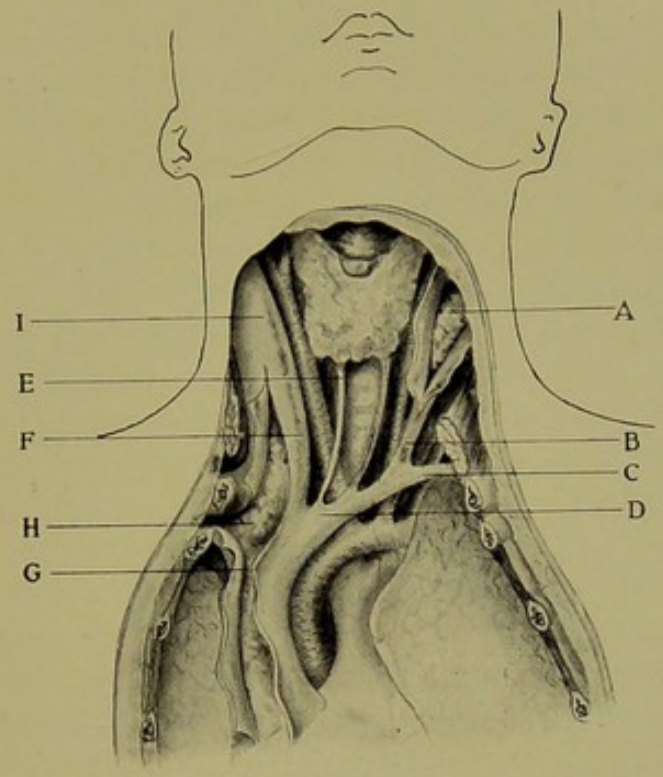


FIG. 10

Illustration representing the thrombosis of the veins in Case 3.

A. Soft clot in the left distended internal jugular vein.
B. The same vein containing firm clot.
C. Left subclavian vein.
D. Left innominate vein.
E. Inferior thyroid vein.
F. Right innominate vein.
G. Superior vena cava.
H. Right subclavian vein.
I. Right internal jugular vein.

The external jugular veins are not shown.

condition of a very acute rheumatic carditis. As regards the pericardium the vessels in the subserous areolar tissue of the visceral layer were extremely congested and the areolar tissue surrounding them was much swollen and hyaline in appearance. The superficial connective tissue layer contained numerous inflammatory cells, and, finally, there was an adherent layer of lymph, the serous epithelium having disappeared. The same process could be traced throughout the heart wall along the course of the vessels ; there was the same swelling of the connective tissue supporting them and the same inflammatory cell exudation which could be traced even between the muscle fasciculi and the capillaries between the fibres were dilated. Immediately beneath the pericardium the process was quite distinct and there was loss of striation but no gross change was apparent in these superficial layers as compared with the deeper. The muscle fibres, with their nutrition altered thus and supplied by blood probably toxic with the rheumatic poison, must necessarily have suffered throughout the heart wall. Sections taken through a papillary muscle, with its chordæ and a part of the mitral valve, showed very markedly this interstitial inflammation. The soft clot in the superior vena cava was hardened and sections were cut, but no organisms were discovered. A series of sections were made from the right brachial vein to the axillary, from a region not affected to a region definitely so. Sections of the vein showed the clot gradually permeated by spindle and round cells, with formation of a network, the adhesion of the clot to the wall of the vein first at one place, then at several, by means of branches spreading in from the intima, and finally the formation of canals lined with spindle cells. In these sections the vein wall was not noticeably thickened, but as the thrombus became more firmly attached there was evidence of early phlebo-sclerosis. Doubtless the lowest portion of the internal jugulars would have shown this process more definitely. No micro-organisms were found either in the clot or in the vein itself. A section from the left brachial showed a small adherent thrombus at one point, slightly diminishing the lumen of the vessel.

Owing to the detail in the description of the cases given above it may be well to review them briefly as they are unquestionably of different value. The first case is incomplete—

clinically because the patient was such a short time under observation and pathologically because, ignorant of the rarity of the condition, no minute observations were made. The second case is an unusual one, resembling very closely malignant endocarditis. It is included with the other two because no micro-organisms were found upon the valves and more especially because, the ætiology of acute rheumatism being still obscure, the exact place which malignant endocarditis must take in relation to it must still be uncertain. Having pointed out the gradual onset, the continued pyrexia, the sweating, infarction, and ulceration of the chordæ tendineæ, it is an open question as to whether or not the condition is comparable to that of the other two cases. The third case is by far the most complete, for the diagnosis was made some days before death and the symptoms were accordingly studied with more precision. The remarkable similarity in the distribution of the thrombosis in the first and third Cases has been alluded to earlier in this article.

In a comprehensive paper by Gatay on *La Phlebite Rheumatismale*[1] two views are put forward in explanation of rheumatic thrombosis. One is that of Schmidt, who considered the thrombosis primary, and the other is that of Letulle and Gatay, who considered a rheumatic phlebitis to be the first event. Confining attention to the cases mentioned above, it seems to us impossible, so long as the exact ætiology of rheumatic fever is obscure, to decide which process was the initial one. It is certain that the blood-current was feeble, for the heart muscle was distinctly affected in two cases and in all there was much organic disease with tricuspid incompetence ; the blood was altered, for there was profound anæmia, and both these conditions predispose to thrombosis. On the other hand, the veins most affected were those in which the circulation was aided by gravity, especially as there was orthopnœa. The thrombosis however was most advanced where the vertical current in the jugular stream met the more or less cross current in the subclavians. Again, in two cases there was active carditis, which suggests the possibility of phlebitis, and in one case there was periphlebitis. Nevertheless apart from the periphlebitis the changes found were not in favour of a primary phlebitis. So much, in fact, depends upon the exact nature of the rheumatic process that in such

complicated cases as these are it seems hazardous to dogmatise.

The duration of the thrombosis is a point which has considerable practical interest. The changes in the axillary vein described above pointed to a duration of at least eight days and the condition in the jugulars was of considerably longer standing. Now in both the cases under observation for some weeks there was varying œdema of the face, noted from the time of admission, an occurrence which is not common in cardiac disease. Again, sections of one vein showed in some places clot adherent in one place only, whilst elsewhere the lumen was free. These facts point to the possibility of a gradual thrombosis having occurred during a period of weeks, with exacerbations when the disease flared up, producing finally arrest of the circulation. It is possible that œdema of the face, which is more commonly observed in the advanced morbus cordis of children, may in some cases, depend upon the occurrence of a partial thrombosis of this kind.

The diagnosis offers some difficulty. In the third case, Dr. Cheadle pointed out the close resemblance in the appearance of the neck to severe parotitis or to angina from severe throat affections. Again, when there are blood and albumin in the urine the œdema and pallor of the face are very suggestive of Bright's disease. The distinctive features are the local appearance and spread of the œdema, the marked tenderness, and the extreme swelling and in the severe cases, pain on moving the head. The feeling of the firm cords in the neck is convincing, but not an easy observation because of the danger of any but the lightest manipulation, and also the tenderness and the rigidity of the inner heads of the sterno-mastoids. Mental apathy is a remarkable symptom. The prognosis of these cases, apart from the thromboses, is exceedingly grave, and that they introduce an additional element is shown by the occurrence of aphasia and a gradual coma in the first case and sudden dyspnœa and pulselessness in the second. The treatment must necessarily be considered from the view of the general condition present, and great care in moving the patient is necessary where there is this additional complication.

Thrombosis in rheumatism is one of the rarer features of this disease. Dr. Archibald Garrod in his treatise on Rheumatism

makes a very definite allusion to it and quotes the researches of Schmidt and Letulle upon the condition. Dr. Cheadle mentioned other cases he had met with. Gatay in his paper in 1896 describes two cases with necropsies; one (Macaigne and Lauren's case) showed small-celled infiltration of each coat of the vein and desquamation of the endothelium followed by an inflammatory change in the vessel wall. Bacteriological results were negative. In this case thrombi were found in the brachial, axillary, and subclavian veins. Renouard noted difficulty in turning the neck in one case. Gatay states that it can attack the veins of the neck, but it is exceptional for it to start in the jugulars. One case is quoted where a thrombus was found in the external jugular only. Macaigne and Laurens noted in their case the heavy mental state. Petechiæ, erythemata, and fever are pointed out as occurring simultaneously with the thrombosis and the veins may be arborescent in the neighbourhood. It would appear from the literature on the subject that the veins of the extremities especially of the lower are most frequently affected. Two of the cases recorded above certainly appear to be quite remarkable both in their similarity and the great extent of the thrombosis.

[1] *La Gazette Hebdomadaire de Médecine et de Chirurgie*, February 1896.

PAPER NO. VI

THE HISTOLOGY OF THE RHEUMATIC NODULE

By F. J. POYNTON, M.D., and G. F. STILL, M.D.

(*Transactions of the Pathological Society of London*, 1899.)

The chief interest of this paper, written with Dr. G. F. Still, lies in the demonstration of the fact that the structure of the rheumatic nodule is essentially compatible with that of a lesion produced by an infective agent. Insignificant though this manifestation of rheumatism may appear, it is well recognised as a very characteristic result of an acute rheumatic process, and had this investigation discovered the structure to be unlike those of the other manifestations, it would have given rise to considerable difficulties in explanation. It is an illuminating fact, however, that, associated as the nodule usually is with severe rheumatic heart disease, the structure should be strictly comparable to the focal lesions in the myocardium ; and also in the pericardium, and other serous membranes, in severe rheumatism. Another interesting point is the bearing that nodules of this kind may have upon the explanation of the deeper focal lesions in the muscles that occur in some cases o muscular rheumatism.

In bringing before this society a paper upon the histology of the rheumatic nodule, we are fully conscious that its structure has been already described in detail by many excellent observers ; but we venture to think that the descriptions which have been given, especially in the text-books of medicine, are based upon appearances that are found when the nodule has already passed through the earliest stages of its formation, and for that reason undue stress has been laid upon the fibrous elements which are then so evident. The essential character of the nodule is to be judged from its earliest appearances, before the morbid effects of the rheumatic poison have been modified to any considerable extent by the reactive processes

that occur within the body ; and it is from a study of these earlier phenomena that one sees most clearly the closeness of the analogy, perhaps the actual identity, which exists between the rheumatic process, as seen in endocarditis and pericarditis with that seen in the nodule, a relation pointed out long ago by Dr. Barlow and Dr. Warner.

It is, then, to the earlier phenomena that we desire to call attention, and the sections shown have been selected as illustrating this stage of nodule formation, and of the allied processes in the endocardium and pericardium.

We may perhaps first be allowed to make a few general observations upon the difficulties that are met with in preparing sections of the rheumatic nodule, and to call attention to certain staining processes which are of value in such an investigation. In the first place, as already pointed out, it is necessary to take the newer formations, and not those of many weeks' standing, and to ensure this it will probably be necessary to take the smallest that can be obtained. Further, the section must pass through or at least near the centre of the nodule, for, as has been repeatedly demonstrated, the microscopic appearances at the periphery are very different from those at the centre. It is probable that the difficulty in carrying out these precautions account in some degree for the discrepancies in the descriptions which have been published. Finally, certain colour reactions given by the aniline dyes carbol-thionin and carbol-gentian violet give considerable assistance in the study of the early formation of the nodule.

The value of thionin as a nuclear stain was first pointed out by Martin Heidenhain in the " Festschrift für den fünfzigen Jahren Jubillaume Herrn Dr. Kölliker." [1] If this stain be used for recent fibrinous exudations, such as occur in rheumatic pericarditis, or in pleurisy, it is found that the exudate stains a pale-blue colour, in contrast to the violet blue of the nuclei of the cellular elements and fibrous tissues. If this exudation be stained by Weigert's fibrin method it will be also seen that the carbol-gentian violet gives the usual reaction for that material.

So far as the naked-eye appearance goes, the smallest nodules which can be appreciated either by sight or touch during life are by no means the smallest which can be seen after death. It was noted on several occasions that where only a few nodules

could be found on the head during life, numerous minute-deposits of the same yellowish-pink material were visible at the post-mortem. Some of these deposits were more or less rounded in outline, others ran together into irregular areas, each with its leash of small dilated blood-vessels running up to it, the whole being too small to be appreciated during life. The colour of these minute deposits is much less like that of fibrous tissue than that seen in the older nodules, which are greyish white rather than yellowish pink. On attempting to remove one of these smaller nodules there is considerable difficulty, for they contain a certain amount of fluid, exudative in character, and any squeezing or traction diminishes their bulk, so that they are often lost altogether. This difficulty is the greater because there is no distinct line of demarcation from the surrounding fibrous tissue.

Turning now to the microscopic details, we should like to point out the close resemblance that there is between the appearances of an early rheumatic nodule and recent rheumatic peri- and endo-carditis when stained by a precisely similar method.

The sections shown were taken from a case that died in St. Mary's Hospital. Three weeks elapsed between the first visible evidence of the nodule and the death of the patient, and thus, though not in its very earliest condition, it still shows distinctly the nature of the early changes.

All the sections were from tissues fixed in corrosive sublimate, they were cut in paraffin, and stained with carbol-thionin.

In the centre of the nodule there is a homogeneous material arranged in layers and free from cellular elements. This stains pale blue with carbol-thionin and gives Weigert's fibrin reaction with gentian-violet. We look upon this material as fibrin in the interstices of which there was originally fluid. It is the presence of this homogeneous material which we wish particularly to emphasise : for, as we have pointed out below, it is this, and not the subsequently developed fibrous tissue, which is, in our opinion, to be regarded as the essential element in the nodule.[1] Compare now with this the exudation on the free surface of the inflamed pericardium, and the vegetations on the valve, and it will be seen that they have much the same appearance and give the same reaction.

Away from the centre of the *nodule* towards the periphery,

many cellular elements become visible encroaching upon this fibrinous centre; and again comparison with the deeper part of the pericardial exudation and with the valve shows a similar appearance. Still further towards the periphery of the *nodule* fibrous tissue is apparent, some of it swollen and hyaline, and in places there are distended and tortuous vessels. In the deeper part of the pericardium also the distended vessels are very apparent, and the hyaline appearance of its fibrous matrix is also distinct. In the *valve* the swollen appearance of the fibrous tissue can also be detected.

Thus we can recognise in these three sections fibrinous exudation, cellular infiltration, and fibrous tissue, and we know that in the pericardium the sequence of changes is as follows: first, vascular dilatation; then exudation, which in rheumatism is usually fibrinous; cellular infiiltration; and, finally, fibrosis. We conclude that the same sequence of events occurs in the rheumatic nodule.

In this way, and in this way only, it seems to us that the occasional rapid appearance and disappearance of a nodule can be explained, for if the rheumatic process is rapid and evanescent, the fibrinous exudate is as rapidly absorbed, and the nodule, which in such a case is probably not fibrous at all vanishes. If the morbid process be more protracted, then the restorative changes will be slower, and there will be some fibrosis in addition to absorption, and the nodule will more slowly disappear. It is of such a nodule as this that sections can be most easily obtained. Now and again the nodule lasts for many months, and the section of such a one shows imperfect restorative processes, the fibrous tissue is ill-formed and only to be found in patches, a condition which can also be observed in some of the old nodules upon the cardiac valves.

We are aware that it has been suggested that the structureless material is a product of degeneration in the nodule, but this suggestion can hardly, we think, be correct, in view of the fact that the appearance is particularly well seen in the smaller and more vascular nodules which are presumably the young ones, and therefore the least likely to degenerate.

A study of nodules in various stages of development has seemed to us to show that this central portion, consisting apparently of fibrinous exudate, is the basis, so to speak, of the nodule, and it is from this, therefore, and not from the

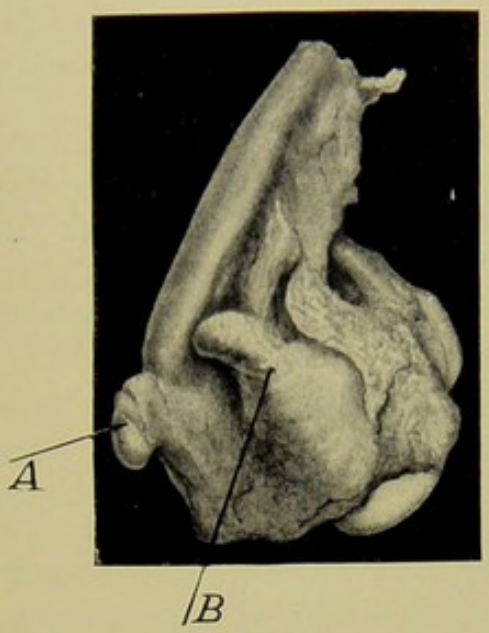


FIG. 11

A dissection of the elbow-joint of a child, showing two subcutaneous nodules.

A. Nodule over the olecranon process.
B. Nodule over the outer condyle.

(From the museum of University College Hospital.)

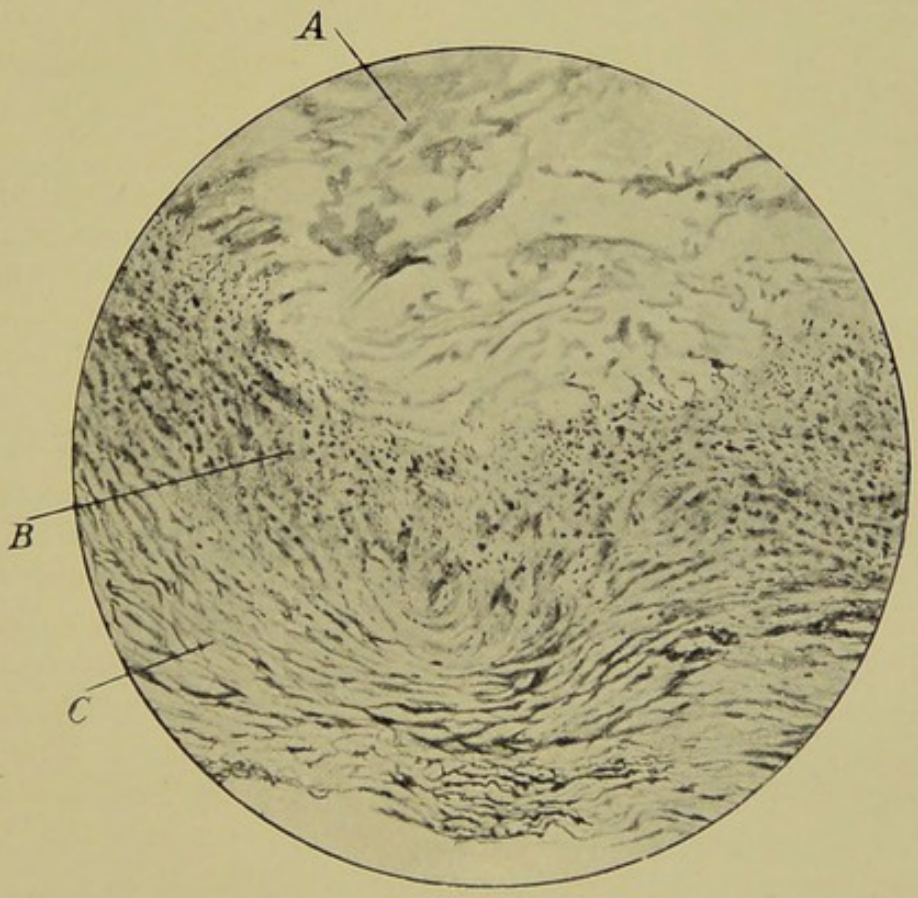


FIG. 12

Section of a rheumatic nodule of three weeks duration

A. Area of fibrino-cellular exudation and necrosis.
B. Area of leucocytic infiltration.
C. Area of swollen fibrous tissue.

peripheral portion, that its essential character must be judged. Moreover, the comparison with the pericardial exudation shows, we think, that the essential change which produces the rheumatic nodule is an actual deposit of inflammatory exudation ; and one might even go further and say that the formation of fibrous tissue is not a necessity : it need not, and certainly does not always occur. This conclusion, is drawn from the microscopic appearances, is confirmed by the clinical fact that a nodule may appear in twenty-four to forty-eight hours, and the whole time from appearance to disappearance may, it would seem, be only three days.

Finally, we would suggest, if the occurrence of fibrous tissue formation is to be regarded as a late phenomenon and in no way essential to the formation of nodules, a view which we think is confirmed by the appearance we have described, that it is more satisfactory to apply the term "rheumatic" or "subcutaneous" to these nodules than to call them "fibrous."

[1] Later investigations lead us to modify this statement and to substitute as the essential element of the nodule the deposit of the diplococci in the tissue. We would also add to this description that necrosis of tissue as well as fibrino-cellular exudation occurs in the centre of the nodule.

PAPER NO. VII

A CASE OF VIRULENT ACUTE RHEUMATISM WITH EXTENSIVE PURPURA; TEMPORARY IMPROVEMENT FOLLOWED BY DEATH FROM CARDIAC FAILURE; NECROPSY; MICROSCOPY

(Under the care of Dr. D. B. LEES.)

(Reprinted from the *Lancet*, October 28, 1899.)

The case recorded in this paper was a very remarkable one, and at the time of its occurrence gave valuable indications of the direction for further research. The isolation of streptococci from the blood during life, with the discovery of the endocardial lesions of simple rheumatic endocarditis after death, supplied the first definite evidence we had met with supporting the view that rheumatism might cause both a simple and malignant endocarditis. This case also added support to previous studies of the myocardium, and finally brought prominently before us the possibility that the bacterial agent we were searching for in acute rheumatism was a strepto-diplococcus.

A GIRL, aged 17 years, was admitted to St. Mary's Hospital on January 16, 1899, for purpura and shortness of breath. On the morning of the 13th she had noticed some purple spots about both ankles, followed on the next day by pains in the joints. Upon close inquiry it was ascertained that on the 9th the throat had been sore and that on the 15th there had been a shivering attack. The important facts in her previous history were an attack of chorea five years and an attack of rheumatic fever two years previously.

Upon admission it was evident that the patient was seriously ill; the face was flushed, the temperature was 101.6° F., and the pulse-rate was 120 to the minute. She complained of slight pains in both ankle-joints and the left knee and these

joints were swollen. Both lower extremities were covered with purpuric patches of varied size and upon the outer sides of the legs there were erythematous areas indicative of a fresh outbreak of purpura in these positions. The pulse was regular and easily compressible. The cardiac impulse could not be seen but was felt in the fifth intercostal space almost in the anterior axillary line. The percussion limits of the deep cardiac dullness were as follows: two and a half fingers' breadth external to the left vertical nipple line and two fingers' breadth external to the right sternal margin, the upper limit being the third rib. There was no pericardial friction, but over the region of the impulse there were systolic and presystolic murmurs. The aortic second sound was clear but the systolic murmur audible over the region of the impulse could be traced, though with diminishing intensity, to the tricuspid, pulmonary, and aortic areas. In the left axilla there was pleural friction and there were scattered rales in both lungs. The urine was free from albumin and blood. Neither the liver nor the spleen could be felt. To summarise briefly the condition, it represented the features of a severe attack of rheumatism in a patient who was already predisposed to the disease, the special clinical interest being the marked cardiac dilatation and extensive purpura. The day after admission a sore throat again developed and then the purpura, though fading upon the legs, appeared upon the elbows and forearms. The pleural friction remained constant and the cardiac dilatation increased. The line of treatment that was adopted was application of the ice-bag over the heart when pericarditis appeared and the administration of salicylate and bicarbonate of soda.

During the next week some dullness was discovered at the base of the left lung and the purpura became much more extensive over the arms and also appeared upon the face and abdomen. The patient was now looking very ill and was wasting considerably. The temperature was, however, never high, seldom reaching 101°. On January 24, eight days after admission, general pericardial friction developed and during the next few days the purpura spread over the abdomen and back and became so extensive as to baffle description. In many places there were large sanious bullæ and over the back the epidermis began to give way, leaving raw and painful

surfaces. During this week the liver rapidly enlarged and reached the umbilicus, the respiration rate rose from 28 to 48 per minute, the lungs were congested, and a fatal termination appeared to be imminent. Venesection was resorted to for the relief of the right heart failure, and cultivations, aerobic and anaerobic, were made by Mr. Plimmer and Dr. Poynton of the blood taken from the median basilic vein with every precaution. Upon two occasions a pure growth of cocci arranged in chains was obtained. In one of the anaerobic tubes a bacillus was also present but Dr. Poynton failed to isolate it. It was a point of some interest that where carbolic compresses had been used to the arm for antiseptic preparation purpura rapidly appeared and was very marked, whereas cotton-wool wrapped round the tender joints produced no such effect. The fluid from the bullæ gave a growth of staphylococci Examination of the blood showed no leucocytosis of note.

The pericarditis remained evident for the next three weeks, the extent of the friction gradually diminishing. Throughout this period the patient was extremely ill, the legs became œdematous, the purpura still further increased, and there was orthopnœa with great prostration. By the middle of February there was slight improvement, the temperature rarely reached 100°, and the cardiac inflammation slowly diminished. Digitalis and nux vomica were now given and the improvement was steadily maintained. At this time the most noticeable symptoms were attacks of dyspnœa and blueness, with paroxysms of præcordial pain. By the end of March there was a distinct gain in every way, the purpura had subsided, the skin was healing, and the œdema had disappeared. Good sleep was obtained, and though the area was still very extensive the cardiac sounds had become more defined. During April the patient was able to lie upon a couch daily, but it was evident that she was not gaining flesh, as was hoped, and she complained occasionally of the old pain over the præcordial region. There was no evidence of a relapse of rheumatism and no more purpura developed, but it seemed rather that the damage to the heart had been so severe and the circulatory power so enfeebled that the nourishment of the tissues could barely be maintained even at this low level. On April 12, the pulse became irregular and there was troublesome vomiting. The liver rapidly enlarged and the venous congestion increased.

The patient lingered on for a few days and then died almost suddenly on the 15th from cardiac failure.

A post-mortem examination was made 24 hours after death. The heart was much dilated and the left lung was collapsed and lay hidden behind the left ventricle. The pericardium was adherent, the adhesions being of recent date. Although the area of præcordial dulness had been so extensive yet there was no fluid in the pericardial sac, this being obliterated by the general adhesion. The right limit of the heart occupied by the right auricle did not when traced downward curve inward at its lower part to join the right ventricle, as is normally the case, but extended in a straight line to the diaphragm. This is a fact of some importance, for the inward curve of the right border of the cardiac dullness has been looked upon by some authorities as a useful assistance in distinguishing between pericardial effusion and cardiac dilatation.. When, however, there is great dilatation of the heart this cannot be relied upon, for on this and several other occasions Dr. Poynton has observed this alteration in the contour of the auricle. The cardiac muscle was profoundly altered and of a pale purple colour. The mitral, aortic, and tricuspid valves were all slightly thickened, the mitral to the most marked extent. There was no recent valvulitis, and there was rigidity rather than stenosis of the mitral orifice. In the first part of the aorta there were some patches of aortitis and there was a small infarct in the spleen. The remaining viscera showed the changes usually observed in severe cardiac failure. The pleuræ contained no excess of fluid but on either side there were recent pleuro-pericardial adhesions.

Sections of the heart walls were made in several situations and some of the tissues were fixed in perchloride of mercury and others in Hermann's fluid. Throughout the entire wall, including the papillary muscles, there was extensive fatty change in the muscle fibres. Scattered through the heart wall there was also a cellular exudation between the muscular bundles, which, though not extensive, was definite. A very striking feature in the sections was great capillary dilatation, and though the capillaries are more than usually apparent in fatal cases of actue rheumatism this condition was remarkable.

Considered from the standpoint of the relation of rheumatism to infective endocarditis this case is of some considerable interest. The extraordinary purpura pointed to a profound alteration in the blood such as occurs in septic rather than in rheumatic conditions and the cultivations of streptococci from the blood also supported this view. But the clinical course was that of virulent rheumatism and the necropsy showed results which are associated with rheumatic rather than infective endocarditis. It is in such a case as this that the difficulties in separating these two conditions become apparent. If rheumatism be the result of a specific micro-organism may it not be that infective endocarditis now and again represents some phase of that specific rheumatic infection in which the virulence has become exalted or the resistance altered in some unusual manner? A very clear picture can be imagined of an alcoholic patient becoming the victim of tuberculosis, but it is more difficult to apply this principle of secondary infection to rheumatism and infective endocarditis, for the former disease may produce endocarditis, infarction, purpura, sweating, and fever, and the latter need not necessarily produce suppuration.

Again, apart from the extreme purpura, this case presents features of interest as an example of virulent rheumatism. Thus, pericarditis did not become manifest until eight days after admission, yet from the first the cardiac dilatation pointed to a fresh rheumatic infection. No doubt pericarditis may exist before detection by the friction, but it may well be doubted after the study of such a case as this whether dilatation which so commonly precedes rheumatic pericarditis, is to be explained by any latent pericardial inflammation. That there is slight pyrexia in severe rheumatic affections of the heart is a well-recognised clinical phenomenon and of much interest now that fever is more and more looked upon as an evidence of reaction to infections. The enfeebled circulation may have some profound influence—a chemical one—in preventing this reaction: a condition perhaps comparable to the low temperature and feeble heart of the pneumonia in alcoholism and to the last stages of severe septicæmia. The attacks of præcordial pain during the period of improvement were compatible with a severe myocardial affection, and the necropsy proved that it could not be due to a previously

thickened and generally adherent pericardium. The marked fatty degeneration of the muscular fibres has doubtless an important meaning. This change in the cardiac muscle is frequently regarded as due to an impaired circulation. It is, however, much nearer to the truth to speak of it as due to a poisoned circulation, for it is found in alcoholism, typhoid fever, diphtheria, and in other infections. In diphtheria the condition of the heart wall may almost precisely resemble that found in rheumatism, and there is but little doubt that diphtheria acts directly upon this structure.

PART II

THESE PAPERS DEAL WITH THE DEMONSTRATION OF THE BACTERIAL CAUSE OF ACUTE RHEUMATISM, THE NATURE OF THE RHEUMATIC PROCESSES IN MAN AND ANIMALS, THE BEARING OF THE RESULTS OBTAINED UPON CONDITIONS ALLIED TO THE RHEUMATIC, TOGETHER WITH SOME INVESTIGATIONS INTO SUCH CONDITIONS

SUB-GROUP A

PAPER NO. VIII

THE ÆTIOLOGY OF RHEUMATIC FEVER

(Reprinted from the *Lancet*, September 22, 1900.)

This paper was the result of an investigation extending over two and a half years, during which time Westphal, Wassermann, and Malkoff published their results from the investigation of a fatal case of acute rheumatism with chorea. Progress was slow for two chief reasons. We had been led by the fact that Triboulet had relegated the position of the diplococcus which he had investigated to a secondary position in the pathogenesis of the disease, to commence with a search for Achalme's bacillus. During this search we discarded on several occasions the very micrococcus we now believe to be the true excitant of the disease. Then for twelve months we failed to demonstrate the diplococcus in the human tissues and only succeeded when we obtained experimental carditis. Taking advantage after this of the thin parietal pericardium of the rabbit, we were able by suitable methods to look along the capillary blood-vessels, and thus trace the escape of the micrococci into the tissues and study their subsequent fate. This paper was the basis of our subsequent investigations, for it was laid down upon the broad lines of clinical, pathological, bacteriological, and experimental evidence. From the first we recognised the pitfall of looking upon the bacterial cause of a specific disease, and a specific test for a bacterium in vitro *as identical problems. At the time of publication the elementary conception of the streptococcal group added considerably to the difficulty of combating the view that we were working with a contamination or with a secondary infection.*

THE ætiology of rheumatic fever has proved to be a problem of such complexity that it is necessary to state at the very outset of this paper the scope and object of the research. The various results that had been already obtained by investigators were in themselves our first difficulty, for they necessitated the employment of widely different methods to enable us to cover the ground already traversed. Our first intention was

to obtain, if possible, some definite facts from which as a basis we might make further advances, and the discovery and isolation of micro-organisms in the form of diplococci in eight sucessive cases of rheumatic fever afforded us this opportunity. When we had obtained these diplococci in pure culture Mr. H. G. Plimmer undertook a series of inoculations into animals and the results that followed provided us with further data. Finally, microscopic investigations of the human and animal tissues have been another source from which we have obtained facts which we believe to be of considerable importance. The methods that have been used and the conclusions that have been obtained from these three sources are detailed in this paper, together with a brief historical survey of the work of others upon this subject.

There are many points of interest that are suggested by these results ; but the most important fact deducible from our researches, as detailed below, is *that this diplococcus which we have isolated is a cause of rheumatic fever.* It is to this conclusion that our results seem irresistibly to lead. We are not, however, in the face of the results of others, in a position to state that these diplococci are invariably present in rheumatic fever, nor are we able to claim that they are the only cause of this disease.

An Outline of the History of the Bacteriology of Rheumatic Fever

Before giving an outline of our results a historical survey of the subject is appended sufficient to indicate the various views that are, and have been held, and to do justice to others who have made investigations upon this question. This outline cannot claim to be exhaustive, but it does, we hope give due credit to those who have already expended much labour in attempting to discover the true cause of rheumatic fever. Dr. A. Mantle in 1886, described and pictured a diplococcus in the blood of cases of rheumatic fever, and advanced the theory that the disease was of microbic origin. In 1892 Fraenkel [1] called attention to a paper by P. Guttmann upon the ætiology of rheumatism and its complications Guttmann described a case of very acute rheumatism with exudative pericarditis complicated by abscesses in the kidneys and muscles from which the staphylococcus pyogenes flavus

was isolated. This micro-organism was obtained from the pericardial exudation and the abscesses but not from the joints. Guttmann expressly stated that this was not a case of true rheumatism, nor did he consider this organism, if it were the cause of the rheumatism in this case, to be the sole cause of rheumatic fever. Leyden also concurred with this opinion. In the same year Sahli [2] discovered the staphylococcus pyogenes citreus in the synovial membrane of the joints in a case of rheumatic fever and also in the pericardial exudation. He considered rheumatic fever to be due to a staphylococcic infection but left it an open question as to whether or not the condition was due to an attenuation of the organism. Netter[3] also isolated a streptococcus from a case clinically resembling rheumatic fever but following acute suppurative otitis media. Lanz[4] in 1893 published a paper upon experimental results connected with suppurative polyarthritis. From the pus of an abscess of the brain operated on by Kocher he isolated a bacillus. This on intravenous injection into rabbits caused death in 23 days. Suppurative polyarthritis resulted and the bacillus was again isolated from the joint. To this organism he gave the name of bacillus pyogenes fœtidus liquefaciens. In 1894 Maragliano [5] obtained diplococci and staphylococci from a case which commenced clinically as rheumatic fever and ended as a septicæmia. This writer also insisted upon the relationship between rheumatic fever and suppurative affections. At this time Chvostek[6] and Singer[7] published papers upon the micro-organisms found in the urine of patients suffering from rheumatic fever. Singer found as the result of the examination of the urine in 17 cases that the staphylococcus pyogenes aureus was frequently present, and when present was to be found in considerable numbers, but became less as the disease declined. He associated this occurrence with the rheumatic process. Chvostek, though recognising the importance of Singer's investigation, doubted the validity of his conclusions. Dana[8] in 1894 isolated a diplococcus from a case of chorea following rheumatism. The organism was found in the meninges of the brain and spinal cord. Charrin[9] found streptococci in cases of rheumatic fever. Sacaze[10] made the interesting suggestion that some external wound, often insignificant, might be the site of infection in rheumatic fever. In 1896 Lubarsch,[11] in a paper

upon the streptococcus group and the diseases caused by them, alludes to an exhaustive paper by Buss of Bremen upon the relation of angina faucium to rheumatic fever. Buss[12] in this paper came to the conclusion that the throat and intestines are in many instances the sites of the entrance of the rheumatic infection.

The clinical importance of the angina faucium that occurs in rheumatism had long been recognised. It was mentioned by Trousseau[13] in his "Clinical Medicine" and Dr. Kingston Fowler[14] in 1880 published an account of 20 cases of acute rheumatism ushered in by tonsillitis; Dr. Cheadle[15] further insisted upon this clinical fact in 1888 in the Harveian Lectures upon the rheumatic state in childhood.

Achalme[16] introduced a new field for investigation by a series of papers upon the bacteriology of rheumatic fever dating from 1891. He discovered a bacillus in the blood of patients who succumbed to rheumatic fever and by his subsequent researches confirmed this observation. His results are of such importance that some space must be devoted to an account of them. The bacillus resembled that of anthrax both in size and in the blunt ends, but varied considerably in size though not in thickness in different media. It occurred in the blood in scanty numbers and was grown anaerobically, not aerobically. A mixture of milk and beef-tea was the medium used, but it grew well upon alkaline bouillon made from horses' flesh. The anaerobic tubes were not opened for from eight to ten days. Solid media were not well adapted for studying the properties of this bacillus. When growing in alkaline bouillon gas bubbles and a turbid deposit appeared within 12 hours. The bacillus stained well with all the aniline dyes but best with faintly alkaline methylene blue. In 1897 Achalme[17] published a detailed account of his researches upon this bacillus with clinical histories of nine cases in which it had been found. The results of injections into animals were also given. Sanious exudation at the sites of inoculation was a prominent feature and in the most severe cases death occurred from septicæmia. A true picture of rheumatic fever, as it occurs in man, did not appear to result in animals thus infected. The results that Achalme obtained have naturally aroused considerable interest, and it is remarkable that an organism of such a size and one that stains so well should have been

overlooked by those who have investigated the tissues in rheumatic fever.

Thiroloix,[18] following Achalme's investigation of this bacillus, in a series of papers fully confirmed his results. In addition, in five cases of rheumatism he obtained this bacillus and inoculations into rabbits gave the entire picture of rheumatic fever. Again, he obtained the organism from the blood and pleural effusion in one case of rheumatic fever, and this produced in guinea-pigs sanious exudations and in rabbits a heart but not a joint inflammation. In two later cases he obtained the latter also. Triboulet[19] in a case of rheumatic fever found a bacillus resembling that described by Achalme. But later Triboulet and Coyon[20] found a diplococcus in five cases. In two of these the diplococci were associated with Achalme's bacillus, and they argue that severe and complicated cases are due to Achalme's bacillus together with the associated diplococci, whereas the simple cases of rheumatism are due to the diplococci alone. Riva[21] in 1897 isolated a specific micro-organism from eight cases of rheumatic fever. The organism varied much in shape in different media and occurred in both coccal and bacillary forms. He made use of a complicated medium slightly acid in reaction, an essential constituent of which was the synovia from the joints of horses. In 1898 Apert and Triboulet [22] obtained some remarkable results by the inoculation of a rabbit with a diplococcus isolated from the blood of a patient suffering from rheumatic fever. Twenty days afterwards they found thickening of the mitral valve with hypertrophy and dilatation of the chambers of the heart and excess of clear fluid in the pericardium. There was also pleurisy but no peritonitis. None of the joints were affected. This diplococcus was identical in character with that found in 11 other cases of rheumatic fever. In spite of the absence of any joint lesions Triboulet considered this organism to be specific. Injected under the skin Apert found the diplococcus produced a local induration. Bettencourt[23] in 1898 supported the researches of Achalme and Thiroloix. Gustav Singer[24] in a monograph gave the results of an extensive investigation of many cases of rheumatic fever and was led to the conclusion that acute rheumatism is not a specific disease but owes its origin to streptococcal and staphylococcal infection.

In 1889 Kronenberg,[25] in a paper upon angina faucium

in acute rheumatic fever, expressed doubts that rheumatism is a disease *sui generis*, but he thought rather that it was a peculiar reaction of the joints and other tissues to a series of bacterial influences—as, for example, the gonococcal, the streptococcal, and the allied infections. In 1899 Westphal, Wassermann, and Malkoff published a paper, "Ueber den Infectiösen Charakter und den Zusammenhang von Acutem Gelenkrheumatismus und Chorea."[26] Westphal narrated the history of the case from which the material was obtained. It was a severe case of chorea that followed acute rheumatism, occurring in January 1899. Violent delirium with hyperpyrexia and collapse resulted in death on February 24. The necropsy a few hours later showed minute vegetations upon the mitral valve and parenchymatous nephritis; there was no suppuration. Cultures were made from the heart's blood, pericardial fluid, mitral valve, spleen, and brain. Wassermann, after alluding to the resarches of Löffler, Michaelis, Eberth, Litten, and von Leyden, described the bacteriological results. A diplococcus resembling morphologically that found by von Leyden in rheumatic valvulitis was isolated and in 80 rabbits produced fever and multiple arthritis. This organism appeared as a diplococcus in the tissues but grew in culture as a streptococcus. The number of micro-organisms in the tissues of the patient was very small. It required a higher degree of alkalinity than that of the ordinary media, upon which it refused to grow. The incubation period was from three to ten days. All the tissues of the joint were inflamed and in the fluid of those which had been affected longest there was a considerable number of leucocytes. In addition there was exudation in the tendon sheaths and bursæ. The micro-organism was found in the arthritic exudation and cultures from the animals reproduced the disease in other animals. Litten[27] at the same date isolated from a malignant form of rheumatic endocarditis (non-suppurative) a very minute streptococcus which was fatal to mice and guinea-pigs but rapidly lost virulence upon culture. In a footnote to his paper he is of opinion that Westphal and Wassermann have probably found the true excitant of acute rheumatism but suggests that there may possibly be more than one. It appears to us that this diplococcus must resemble, if not be identical with, that investigated by Triboulet in 1897.

This brief survey is sufficient to show how complicated

and uncertain the present position of the bacteriology of rheumatic fever still remains. In the following short analysis of the various hypotheses we hope to make clear that view of the subject which seemed to us the most probable and to indicate the direction in which our researches tended. There may be some who still decline to regard rheumatic fever as a microbic disease, but we have started upon the assumption that it is an infection, being led to this conclusion by the results of clinical and pathological experience and teaching. The broad clinical view of rheumatism which has been taken by such authorities as Dr. W. B. Cheadle, Dr. Thomas Barlow, Dr. D. B. Lees, and Dr. A. Garrod in this country appears to us to support this hypothesis very strongly.

View No. 1. Allowing that the cause of rheumatic fever is microbic, one view that has met with considerable support maintains that there is no specific micro-organism, but that rheumatism is but a form of septicæmia which owes its origin to staphylococcal and streptococcal infection. The close analogy between the rheumatic processes and those of pyæmia and the frequent discovery of staphylococci and streptococci in cases of rheumatic fever have naturally led to this view. It is undoubtedly a very important one and involves bacteriological and clinical problems of the greatest difficulty. It raises the question of what is really the definition of the specificity of an organism and deals with what is still an unknown quantity —viz., the extent of variability that is possible in a micro-organism and its results under varying conditions of virulence and resistance. We have fallen back upon the teaching of clinical medicine and pathology as our guide in this matter. Rheumatic fever as we meet with it in England is a common disease with, on the whole, very definite characteristics. However virulent the disease it may be practically asserted from the clinical standpoint that suppuration does not occur. Many cases die in the course of a year with acute cardiac inflammation, yet the heart and other viscera do not show abscesses. We were inclined to expect that an organism the cause of rheumatic fever if isolated and inoculated into suitable animals would produce in them a condition resembling the rheumatic fever of man in the absence of multiple foci of suppuration. That this limit may be overstepped both in man and animals under exceptional, and perhaps as yet

unknown, circumstances seemed to us very probable, but the general and average result that we expected was a condition in which the absence of suppuration would be a prominent feature.

View No 2. Another view maintains that the cause of rheumatism is a specific diplococcus. It is to this view that we inclined, though we would repeat once more that the definition of what is meant exactly by "specific" involves many difficult problems concerned with the virulence of the infection and nature of resistance.

View No. 3. A third view maintains that the cause is a specific bacillus. This view is a decidedly simpler one, if it were proved to be true. If the bacillus, as for example, that described by Achalme, be found to be invariably present in rheumatic fever it is easily distinguishable from the staphylococci and streptococci that are found so frequently associated in rheumatism, and its morphological characters alone would be of the greatest assistance in establishing the truth of its claim.

View No. 4. A fourth view raises the question of a mixed infection of bacilli and micrococci, an analogy to which is readily supplied by diphtheria. To us this view appeared one of great difficulty and withal unsatisfactory. There can be no reasonable doubt in the face of the numerous investigations that have been made that micrococci of some form or other are frequently present in rheumatic fever and hence the origin of such a view as the one under consideration. Nor can there be reasonable doubt that they are capable of producing polyarthritis, valvulitis, pericarditis, pyrexia, sweating, infarction, and other manifestations closely resembling those of rheumatic fever. If then, both the bacilli and micrococci are needful to produce rheumatic fever the association must be a mysterious one. If the micrococci are the cause of the symptoms it is possible that they are restrained from causing suppuration by the presence of the bacilli. If the bacilli are the cause of the symptoms it is possible that they produce them only when associated with these micrococci, though this is difficult to realise when it is remembered that the latter may themselves produce almost similar lesions.

View No. 5. This last view holds that rheumatic fever is not a disease *sui generis* but a particular reaction of the tissues

to varied infections. We thought that the remarkable constancy of the clinical symptoms of rheumatic fever, as met with certainly in England, were much against its being a condition that would result from many and varied infections.

Not only is there this diversity of opinion regarding the organism, but opinions differ also as to the explanation of the way in which the symptoms are caused. Does the micro-organism remain localised to one spot—for example, the tonsils—and pour its toxins into the system, giving rise in this way to carditis, arthritis, nodules, and other local lesions ? or is it widely distributed and present in the local lesions ? We inclined to the belief that the organism was to be found in the local lesions, though perhaps only with great difficulty. The probability of its occurrence at these sites seemed to us to be indicated by the analogy of pyæmia.

To summarise our point of view at the start of this investigation we thought it most probable that the organism would always be present in cases of rheumatic fever ; that it would be capable of isolation ; that it would produce the symptoms of rheumatic fever in a suitable animal ; and that it would probably exhibit some definite peculiarities upon culture. We also thought that it would be present in the local lesions and that the infection would be a simple and not a mixed one. The analogy that there appears to be between rheumatic fever and septic infections pointed to the infection being micrococcal rather than bacillary. We were, however, naturally influenced by the positive results of Achalme and his corroborators, and their results appeared to us so definite that we gave especial attention to the discovery of this bacillus in our earlier cases.

The Outline of the Investigation

After this brief consideration of these various theories we give in outline the results of our investigation, then in detail the methods, cases, and bacteriological investigations, and finally a short summary of the facts which have been established with some concluding remarks.

In January 1899, we undertook the study of the bacteriology of rheumatism with the intention of confirming, if possible, the results obtained by Achalme. For some long time we were influenced by this intention, but finally abandoned the

attempt, having failed to obtain a bacillus morphologically resembling anthrax either in culture or in the tissues. On the other hand, we obtained later in eight successive cases a diplococcus which grew in liquid media in streptococcal chains. This organism did not thrive upon ordinary agar or serum agar, and though we were able to grow it eventually upon blood agar it appeared to grow best in a liquid medium of milk and bouillon rendered slightly acid with lactic acid. Upon three occasions we isolated the organism in pure culture from the blood of patients during life who were suffering from acute rheumatic pericarditis. It was also obtained from the pericardial fluid after death and from the cardiac valves and lastly from the throat of a rheumatic patient. In our first two cases we did not investigate the characteristics of the diplococcus and in one recent case it was associated with numerous small bacilli. In one case a sarcina was present as a contamination. In five of the eight cases it was in pure culture. When we became acquainted with the researches of Wassermann, Westphal, and Malkoff, it seemed clear that this was the organism they had described, and we feel no doubt that it is identical, although there have been certain differences in the results that we have obtained. As stated above, we succeeded best in cultivating it in an acid medium and have not had success with a strongly alkaline medium, as recommended by Wassermann, though we are in doubt as to the exact degree of alkalinity that Professor Wassermann found to be most suitable, about which point he made no definite statement of which we are aware. It is of considerable interest that we succeeded in growing the diplococcus on two occasions in the pericardial exudation and noticed in one of these instances an increase in flakiness of the fluid. On both these occasions the pericardial fluid was distinctly acid, so that there is this proof that the organism will grow in an acid medium. The demonstration of these diplococci in films from the pericardial fluid after incubation is very definite, and we have also found them in scanty numbers in films from recent vegetations, from unincubated pericardial fluid, from blood from the heart, and from the throat. Their demonstration in the tissues is by no means easy. We have however, demonstrated them unmistakably in the tissue of a rheumatic nodule and in the valves, pericardium, and tonsil. Mr. H. G. Plimmer under-

took a series of inoculations for us from the pure cultures that had been obtained and made intravenous inoculations into rabbits with results of which the following is an outline.

The pericardial fluid from Case 4, that of a boy who had died from an exacerbation of rheumatism, gave the first positive result. Three days after inoculation the animal limped upon the left fore leg, the left shoulder-joint was swollen, and the animal had lost flesh. Later the right hip-joint and right-shoulder-joint became affected, wasting continued, and the rabbit died 10 days after inoculation. The post-mortem examination showed excess of clear fluid in the right shoulder-joint and right hip-joint with reddening of the cartilages. The left shoulder-joint contained an opaque fluid which microscopically contained numerous endothelial cells and a few leucocytes. The heart appeared larger than natural, there was an excess of clear fluid in the pericardium, but apparently no evidence of pericarditis or endocarditis. The liver was dark red. In the lungs there were patches of broncho-pneumonia. There was no sign of abscess formation in any of the viscera. The clear fluid from the joints taken with every precaution, was inoculated into milk tubes. Films were also made and a diplococcus was demonstrated and cultivated from this clear fluid. It was also demonstrated in the mitral valve. Thus it will be seen that in some respects our results in this case corresponded exactly with those of Wasserman. A polyarthritis had resulted and the joint first affected contained a fluid in which there were fibrin and some excess of leucocytes, the cartilages of the affected joints were redder than normal, and in none of the viscera were there any foci of suppuration. In one respect there was a difference and this was an important one : we had demonstrated the organism in the mitral valve. *A second rabbit* was inoculated from a culture of the joint fluid. The cultivations upon six blood agar tubes were injected intravenously into this rabbit with the following results. Upon the third day the right knee-joint swelled and the animal had lost 160 grammes in weight, then followed in succession the other knee-joint and the left shoulder-joint, and finally all the larger joints became implicated. The identity of the course of the disease with that in the first case was remarkable and certain further results developed. Seventeen days after the inoculation a

systolic murmur was detected at the base of the heart somewhat superficial in character and the heart was acting with great rapidity. This murmur was detected for two days and then was lost and at the same time the heart sounds became faint. We diagnosed pericarditis with subsequent effusion. The next day the animal died. During the last week of the illness all the joint swellings had disappeared except that of the right knee. The necropsy showed an excess of clear fluid in the pericardium and a fibrinous coagulum in the sac with some roughening of the visceral layer over the large vessels. The right knee was full of an opaque fluid which, as in the first case, contained the diplococci, endothelial cells, and leucocytes. There was some excess of fluid in the other joints but this was clear. Upon the mitral valve there were two small white opacities resembling an early granulation. The liver was dark red and contained some small white areas which were quite firm and slightly raised. The spleen and kidneys were pale but otherwise natural. The tonsils were natural. Microscopic examination of the mitral valve did not confirm the suspicion of endocarditis. The opaque patches in the liver proved to be localised areas of coagulation necrosis. There was no trace of suppuration in the viscera. The myocardium showed well-marked fatty changes in the fibres comparable to the changes demonstrated in the human heart as occurring frequently in acute rheumatic carditis. The culture of the organism was repeated as before and the cultivations upon three tubes injected into *a third rabbit*, but with a negative result. The cultivations upon six tubes injected into *a fourth rabbit* resulted as follows. Four days after the inoculation the right knee-joint swelled and subsequently the right carpal joint and left knee-joint also and there was general wasting. Upon the tenth day we detected a soft murmur which next day we localised as mitral; this disappeared, but on the fourteenth day there was a murmur upon the right side which we diagnosed to be tricuspid in origin. The confirmation of these diagnoses being a matter of great importance upon the same day that the tricuspid murmur was detected the animal was killed. The necropsy showed that two joints contained an opaque fluid comparable to that found in the preceding cases and one a considerable quantity of clear fluid. There was excess of clear fluid in the pericardium. The mitral valve

FIG. 13

A fragment of the parietal pericardium stretched in a film on a slide and dried, stained and cleared, showing a blood-vessel in the parietal pericardium of a rabbit dead of carditis. (Zeiss, obj. $\frac{1}{12}$, oc. 3).

A. Blood-vessel.
B. Wall of the vessel.
C. Pericardial tissue external to the vessel.

Diplococci are seen in each position.

showed a condition macroscopically comparable to that of an early rheumatic endocarditis, and the tricuspid valve showed also, in the very earliest stage, a row of granulations along the border. The condition of the liver resembled that found in Case 2 and the kidneys also showed some white slightly raised areas quite firm on section. The tonsils were unaffected. The microscopic examination showed points of the greatest interest. In the parietal layer of the pericardium, stretched out and stained, we found the diplococci following the course of the blood-vessels in the perivascular lymphatic spaces. We also demonstrated them in the mitral valve and—what by the light of subsequent events was especially noteworthy—we discovered them in the kidneys in great numbers. There were no suppurative foci in the viscera.

The organisms were once more isolated and injected intravenously into a *fifth rabbit.* This rabbit developed polyarthritis, pericarditis, pleurisy, and pneumonia, with slight valvulitis. The animal was killed at the height of the disease and the especial point of interest in the necropsy was the macroscopic appearance of the thoracic viscera. There were plastic pericarditis and mediastinitis, with plastic pleurisy over those parts of the lungs that are contiguous to the pericardium. The liver had the mottled appearance that is seen in a man as a result of severe and acute rheumatic carditis. During the illness the rabbit had passed urine which was acid and contained numerous urates, granular casts, and diplococci. From the contents of the bladder we isolated and cultivated the diplococcus by the usual methods. There was also exudation into the tendon sheaths around the affected joints and the connective tissue near the larger joints had the gelatinous appearance of the nodule in man. We demonstrated the diplococci in the valves, pericardium, joint exudate, liver, kidneys, connective tissues around the joints, and in large numbers in the lungs and pleuræ. It is, we think, impossible not to recognise in this case the extraordinary similarity to the most severe types of rheumatic fever in childhood.

Another case in which some remarkable results occurred was the second of those in which we obtained a pure culture of the diplococcus from the blood of a living patient suffering from rheumatic pericarditis. The organism was grown upon

the acid medium and transferred to blood agar. Intravenous inoculation of a rabbit produced the following symptoms. Four days after inoculation the rabbit had begun to waste and limped upon the right hind leg, and the knee-joint became swollen. This continued for a week, the animal still wasting, but then it improved so much that the limp disappeared. The heart all this time acted very rapidly but there was no murmur. Five weeks after this there was a relapse and both the hind legs became very weak and the animal very emaciated. There did not appear to be any joint swelling at this time. This condition continued for about three weeks and then gradually passed off, and no cardiac murmur was detected at any time. Was this a paralytic phenomenon ? It was a natural suggestion that it might be chorea, but if so, there was not the slightest twitching, only great weakness of both lower extremities that gradually passed away.

A third case which produced an experimental result was that of Case 6. The case was one of severe rheumatic carditis with early pericarditis. Associated with the diplococci there were some short bacilli and the growth in the pericardial fluid was accompanied by an offensive odour. An inoculation of the two organisms into a rabbit proved negative. An inoculation of the diplococci only into another rabbit also proved negative. We were surprised at this result and three weeks later a third attempt was made, though we felt very doubtful that any result would be obtained because of the difficulty of maintaining the virulence of the organism. This rabbit remained apparently well, but three weeks afterwards we found the temperature raised and a definite systolic murmur at the apex. There was no arthritic change, but the murmur remained constant for a week and was more definite than any that we had previously heard. The animal was then killed and the tricuspid and mitral valves were found to be inflamed. There was also a moderate quantity of clear fluid in the abdominal cavity. We demonstrated the organisms in the valves and in the parietal pericardium, throughout which there was a definite cellular exudation.

The next case (Case 7) gave a negative result, but at this we were not surprised, for the pericardium was totally adherent, and though we obtained the diplococci from the granulations of the mitral valve they were in scanty numbers and the growth

was not a vigorous one. No detectable clinical result followed the inoculation of a rabbit in the usual manner.

The last case (Case 8) was that of an adult, aged 32 years, who came to St. Mary's Hospital suffering from an acute "sore throat." The throat was red and had the appearance of a rheumatic angina. There were muscular pains and a history of a previous attack of rheumatic fever. The heart was extensively diseased, both mitral and aortic valves were incompetent, and the action was excited and the præcordial dullness greatly increased in extent. The condition of the heart completely bore out the history of previous rheumatism. A culture was made from the throat in the milk medium and the diplococcus discovered among other organisms. This was isolated by means of blood agar plates and a pure culture injected intravenously into a rabbit. Three days after inoculation there was dyspnœa and the heart was acting with great rapidity. Two days after this a loud mitral murmur developed and the respirations were now extremely rapid. The rabbit died the same night somewhat unexpectedly. The necropsy showed great dilatation of the heart and a large vegetation upon the mitral valve with an adherent antemortem blood-clot filling the left auricle. We demonstrated the diplococci in the granulation, pericardium, and pleural exudation, and isolated them from the blood and cerebro-spinal fluid.

It will be seen from this outline that on four different occasions very definite results have been obtained with rabbits. The results have been supported by demonstration of the diplococci both in the human and animal tissues. In addition to demonstrating the diplococci in the tissues in most of these eight cases we have found diplococci in the heart valves or pericardium in eight other examples of undoubted rheumatic fever, and in the pia mater and brain from a case of chorea with extremely violent movements which proved fatal with but a slight valvular lesion and no pericarditis.

The Outline of the Methods of Bacteriological Investigation

1. *The material for examination.* The materials selected in the human subject for bacteriological examination were : (*a*) the pericardial exudation ; (*b*) the blood from the heart ;

(*c*) the granulations from the valves ; (*d*) the blood from the living subject during an attack of acute rheumatic pericarditis ; and (*e*) the exudation from the inflamed tonsils. The material in the fatal cases was obtained as soon as possible after death and the necropsy was conducted with strict precautions for the prevention of contamination, all the instruments being carefully sterilised. The pericardium was exposed very completely by removing portions of the ribs as well as the costal cartilages upon the left side. The surface was seared with hot irons and any fluid present was drawn up in sterilised pipettes. The point of the pipette was broken off inside the pericardial cavity, the fluid withdrawn, and the pipette at once sealed. The surface of the right auricle was cauterised and the blood withdrawn in a similar manner. Finally, a sterilised suture was passed through the cardiac muscle at the apex and the heart pulled over to expose the left ventricle ; then the posterior surface was thoroughly cauterised and rapidly opened with a sterilised knife, the walls were held apart by forceps, the blood-clot was removed, and the mitral valve was exposed and curetted.

2. *The culture media.* Both liquid and solid media were used. The fluid media were incubated aerobically and anaerobically. The temperature of incubation was 37° C. The following media were used : (*a*) Fluid. (1) Bouillon and milk, acidified with lactic acid ; (2) pork broth made with Chapoteaut's peptone and rendered strongly alkaline (in imitation of Wassermann's medium) ; (3) bouillon of various degrees of acidity and alkalinity ; (4) ascitic fluid ; and (5) cow's milk and human milk. (*b*) Solid media. Agar, serum agar, blood agar, glucose agar, glycerine agar, and egg albumen. The organism grew best anaerobically in an acid medium. It also grew aerobically in the same medium and in blood smeared upon slightly alkaline agar. The anaerobic cultures were made in Pasteur's pipettes, which were exhausted by an air-pump and hermetically sealed. Films were invariably made from the culture used for experimental purposes before the inoculation.

Details of the Clinical Cases and Experiments

The following is a detailed account of the eight cases of rheumatic fever with the investigations made from them.

Case 1. A girl aged 17 years was admitted into St. Mary's Hospital on January 16, 1899, suffering from purpura and rheumatic morbus cordis. This was the second attack of rheumatic fever and in addition five years before there had been an attack of chorea. This case was published in detail in the *Lancet* of October 28, 1899, p. 1163. After a prolonged illness the patient succumbed to severe morbus cordis. A severe attack of pericarditis had developed while in the hospital and death occurred on April 15. At the necropsy, which was made 24 hours after death, the pericardium was found to be adherent, the adhesions breaking down quite easily. The heart was enlarged and both hypertrophied and dilated. There was mitral, aortic, and tricuspid valvulitis. The other viscera showed the changes usually found in association with severe morbus cordis. There was one small infarct in the spleen. Under microsocopical examination the cardiac muscle showed extreme fatty change. Bacteriology. With Mr. H. G. Plimmer upon two occasions we made cultivations from the blood of the patient during life, taking advantage on each occasion of a venesection that had been done for right heart-failure. Both times we obtained from the tubes of the milk medium diplococci arranged in chains. The medium was treated aerobically and anaerobically. The milk tubes were the only media used.

Note. At this time we were intent upon Achalme's researches and did not pursue the investigation of the micrococci. In one of the anaerobic tubes we found a bacillus but were unable to isolate it, and after considerable investigation we came to the conclusion that it was a contamination.

Case 2. A patient, aged 19 years, was admitted into St. Mary's Hospital on December 4, 1899, suffering from pains in the joints and morbus cordis. This was the fourth attack of rheumatic fever. On admission there was advanced cardiac disease. Pericarditis rapidly developed and the patient died three days after admission. The necropsy, which was made 14 hours after death, showed recent pericarditis with turbid fluid in the pericardial sac, moderate stenosis of the mitral valve,

and recent vegetations upon the aortic valve. Under microscopical examination the cardiac muscle showed much fatty change. Diplococci were demonstrated in the granulations of the mitral valve. Bacteriology. The fluid from the pericardium was inoculated into the medium of milk acidified with lactic acid and aerobic and anaerobic cultures made. At this time we were still engaged in investigating Achalme's bacillus and following his directions the anaerobic tubes were left for 10 days. In both the aerobic and anaerobic tubes diplococci growing in a streptococcal arrangement were discovered. These organisms did not grow upon ordinary agar tubes. No inoculations were made into animals.

Note. The strepto-diplococci were not thoroughly investigated, but it was found that an ordinary agar medium was not suited to them.

Case 3. A woman, aged 20 years, was admitted into St. Mary's Hospital, moribund, suffering from severe rheumatic pericarditis and mitral disease. The patient died the same day. The investigation was incomplete. Through a puncture in the pericardium we withdrew some sanious pericardial fluid in a sterilised pipette. Various media were used and from a bouillon tube and the milk medium we obtained diplococci contaminated with sarcinæ.

Note. In this case the diplococci grew in chains in the acid milk medium in a manner precisely similar to that noted in the two preceding cases. Upon ordinary media these organisms failed to grow.

Case 4. A patient, aged nine years, was admitted into the Hospital for Sick Children Great Ormond Street, on October 11, 1899, suffering from dropsy and morbus cordis. There was no definite history of rheumatism and no history of scarlet fever. Upon admission the heart was found to be enlarged and there was evidence of organic mitral disease. There were dropsy, albuminuria, and ascites. The illness was prolonged and the condition for some time stationary, but in March active rheumatism developed and nodules appeared; this was rapidly followed by cardiac failure and death on March 20, 1900. At the necropsy, which was held 36 hours after death, the pericardium was found to contain some recent plastic exudation and excess of clear fluid. The valvular disease was slight but the heart was much dilated and hypertrophied. The

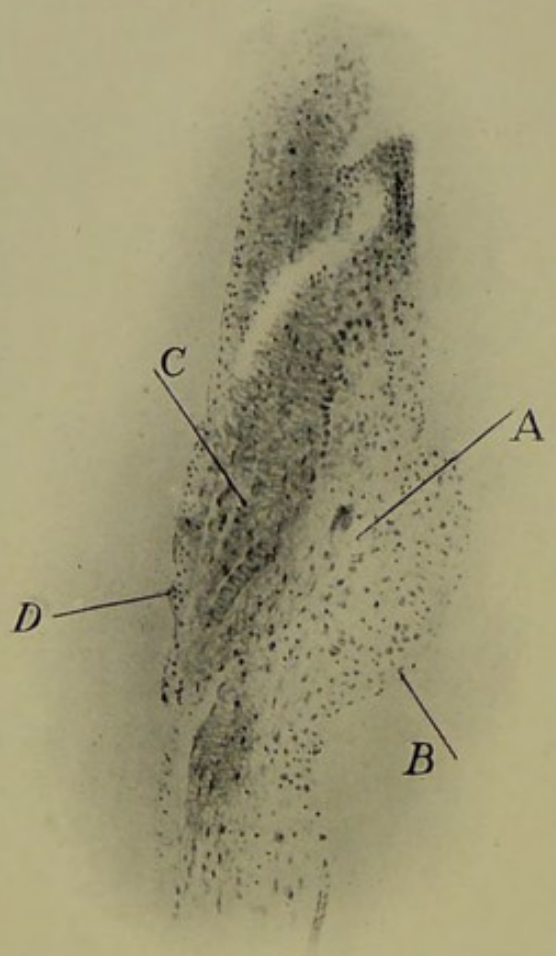


FIG. 14

An early vegetation on a human pulmonary valve in rheumatic carditis. (Low power.)

A. Commencing vegetation.
B. Endocardium on ventricular surface.
C. Connective tissue.
D. Endocardium on arterial surface.
Diplococci were present in the vegetation.

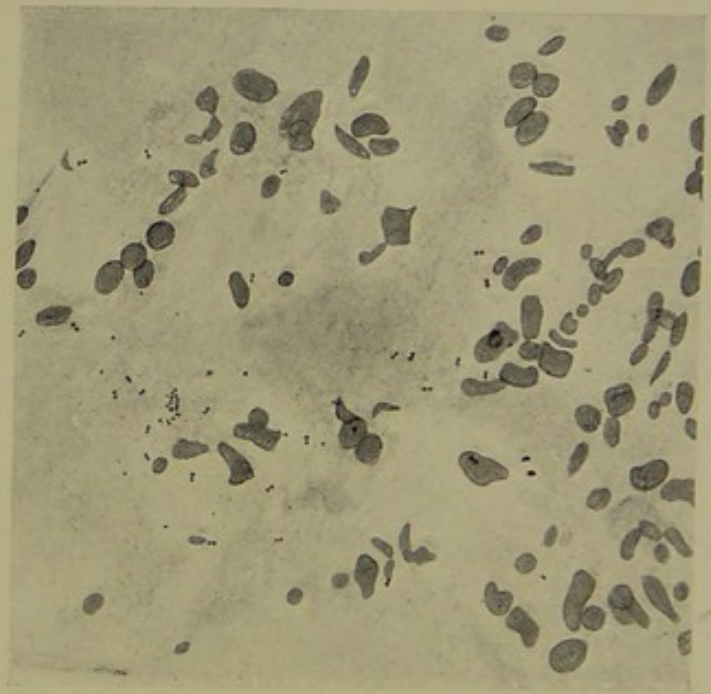


FIG. 15

Section through vegetation on the mitral valve from a case of rheumatic carditis, showing diplococci in the tissues. (Zeiss, obj. $\frac{1}{12}$, oc. 4.)

lungs were œdematous, the liver was "nutmeg" in appearance and the kidneys and spleen were firm. Under microscopical examination the cardiac muscle showed granular and fatty changes and films from the pericardial fluid and heart wall showed diplococci. Diplococci were also found in the mitral valve. Bacteriology. (1) Three Pasteur pipettes of the pericardial fluid were incubated aerobically at 37° C. for three days; and (2) blood-agar tubes were inoculated with the pericardial exudation and curetted granulations from the mitral and aortic valves. The diplococcus was found in every tube in pure culture. On blood agar they grew in discrete and easily detachable colonies. The pericardial fluid had increased in opacity and flakiness. The reaction of the pericardial fluid was distinctly acid and there was no offensive odour. Sub-cultures were made upon the milk medium, but on this occasion they did not grow well. Two tubes of the pericardial fluid were injected intravenously into a rabbit.

Rabbit No. 1. Three days after the injection the animal was wasting and the left shoulder-joint was swollen. Nine days afterwards the right hip and shoulder had become swollen. On the tenth day from the date of inoculation the rabbit died from broncho-pneumonia. At the necropsy the heart appeared enlarged, but there was no definite endocarditis or pericarditis visible. There was a definite excess of clear fluid in the pericardial sac. The cartilages of the affected joints were reddened but there was no ulceration of their surfaces. The right shoulder-joint and right hip-joint contained an excess of clear fluid. The left shoulder-joint contained an opaque fluid and films afterwards showed that the fluid contained many endothelial cells from proliferation of the cells lining the synovial membrance of the joint together with a scanty number of leucocytes. The liver was dark red and engorged with blood. The spleen was firm and the kidneys were apparently natural. There were no traces of abscess formation anywhere. The lungs were solid in patches from broncho-pneumonia. There was no peritonitis. Under microscopical examination the strepto-diplococcus was demonstrated in the joint fluid and the mitral valve which was stained in bulk. The heart showed no fatty change. The spleen and kidneys showed nothing distinctive. Bacteriology. The clear fluid from the right shoulder joint and heart blood

were used for inoculation of anaerobic tubes of the milk medium and 48 hours afterwards these tubes were found to contain the organism growing vigorously in chains. From these tubes six blood agar cultures were made aerobically. The six blood agar tubes were used for the inoculation of the second rabbit.

Rabbit No. 2. Three days after inoculation the right knee joint became stiff and the animal had lost 160 grammes in weight ; four days afterwards the left shoulder became swollen ; five days afterwards both the knee-joints became affected. and the right was more swollen ; 14 days afterwards the animal was much wasted, the heart was rapid and feeble, and the animal was short of breath. The joints still remained swollen. Seventeen days later we detected a basal systolic murmur over the position of the large vessels ; the next day this became fainter and then disappeared. With this disappearance the heart sounds became muffled at the base and we diagnosed as the most probable explanation a pericarditis with effusion. Twenty days after inoculation the animal died. The swelling of all the joints except the right knee had gradually disappeared some days before death. At the necropsy the heart was enlarged and there was excess of clear fluid in the pericardium and also a viscid coagulum. The visceral layer of the pericardium showed slight roughening over the base of the heart. There was no definite endocarditis. The liver was dark red and mottled with white spots of varying size. The spleen was firm. The kidneys showed no definite changes. There was no trace of suppuration in any of the viscera. The affected joints were reddened and except in the case of the right knee contained a very slight excess of clear fluid. The right knee was distended with an opaque fluid which, as in the case of the first rabbit, contained many endothelial cells and also mononuclear and polynuclear leucocytes. The cartilages of the joints were unaffected. The tonsils were not inflamed. There was no peritonitis. Under microscopical examination : (1) in films from the joint the diplococcus was demonstrated in considerable numbers ; (2) the heart muscle showed definite fatty change in many fibres ; (3) the white patches in the liver proved to be liver cells undergoing necrosis ; (4) the pericardial fluid clotted rapidly in the pipette after withdrawal, the clot in the pericardial sac and in the pipette

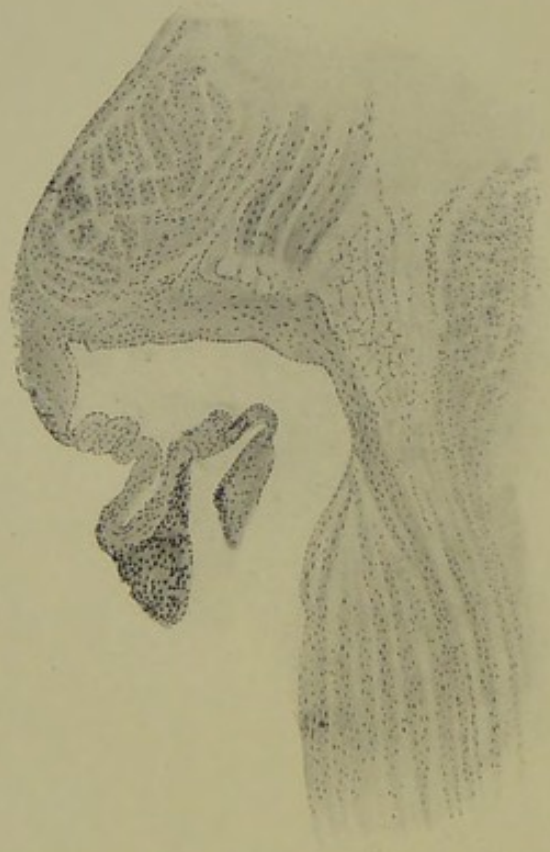


FIG. 16

Section through the auriculo-ventricular junction of the mitral valve of a rabbit, showing under low magnification a commencing vegetation. Above is the auricle, below and to the right the ventricle, to the left the mitral valve (bent on itself in the process of embedding). On the auricular surface of the valve is seen a conical vegetation. Diplococci were present in the vegetation. (Low power.)

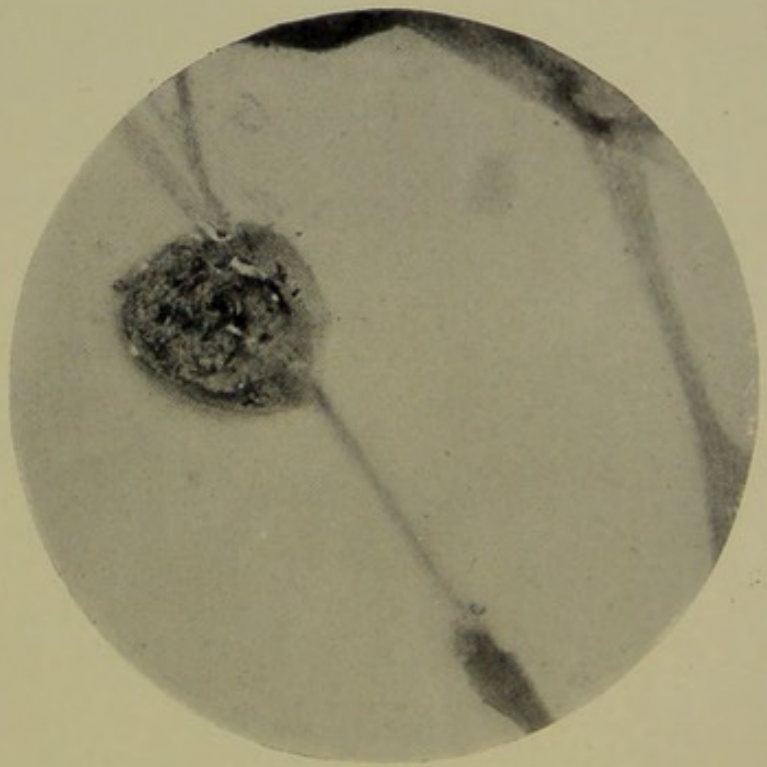


FIG. 17

Microphotograph of a chorda tendinea of the mitral valve of a rabbit, showing local swelling the result of the diplococcus infection. The lower margin of the valve is shown at the upper limit of the figure. This lesion throws interesting light upon the probable changes that occur in the chordæ tendineæ in human mitral stenosis. (Low power.)

showing a delicate fibrino-cellular structure ; (5) the kidneys and spleen showed no change of note ; and (6) there was no peritonitis. There were no foci of suppuration in the viscera. Bacteriology. Cultures were made from the heart blood and right knee-joint in the milk medium and in both series of tubes the diplococcus was found growing vigorously in pure culture.

Rabbit No. 3. A third rabbit was inoculated with the cultivations upon three blood agar tubes but with a negative result.

Rabbit No. 4. A fourth rabbit was inoculated with the contents of six blood agar tubes and symptoms once more commenced to appear on the third day and developed as follows. On the third day after inoculation the right tarsal joint became swollen and tender. On the sixth day afterwards there was wasting and the left knee-joint was swollen. On the seventh day afterwards the right carpal joint swelled. The heart action was excited and we suspected a mitral murmur. The next day this murmur was definite and then became less audible. On the tenth day after inoculation we suspected a tricuspid murmur and the animal was killed to verify these conclusions. For some days previously there had been very marked dyspnœa. At the necropsy the right carpal and tarsal joints were distended with an opaque fluid ; the left knee-joint contained clear fluid. The cartilages were reddened but otherwise unaltered. The pericardium contained an excess of clear fluid. The heart was dilated. There was no visible pericardial roughening. *The mitral valve showed definite granulations, the appearance exactly resembling an early rheumatic endocarditis.* The tricuspid valve showed a still earlier stage. The aortic and pulmonary valves were unaffected. The liver was dark red and mottled with firm white areas, some of them slightly raised above the surface. The spleen was pale but firm. The kidneys were both pale and contained a few white areas, firm and slightly raised above the surface. The tonsils were unaffected. In none of the viscera were there any foci of suppuration. There was no peritonitis. Under microscopical examination (1) *in the parietal layer of the pericardium stretched out and stained in bulk, the diplococci were clearly seen in great numbers along the course of the vessels, lying apparently in the perivascular lymphatic spaces* ; (2) the mitral valve showed on section an early granulation on the auricular

surface, consisting of a proliferation of the connective tissue cells of that part of the valve. The delicate endothelial layer of the endocardium passed over this granulation, and in the granulation and in the deeper part of the endocardium diplococci were visible. They could be seen also in the endocardium lining the auricle and ventricle and causing in places cell proliferation. They were also present in considerable numbers in the retiform tissue at the base of the valve, that is, in the position of the valve ring ; (3) the joint fluid showed numerous diplococci and endothelial cells, also eosinophiles and some polynuclear leucocytes ; (4) the liver showed numerous areas of coagulation necrosis ; (5) the kidneys showed areas of coagulation necrosis, especially in the region of the convoluted tubules and numerous diplococci in these areas ; (6) the heart muscle showed well-marked fatty and other degenerative changes ; and (7) there was no peritonitis. Bacteriology. The diplococci were obtained in pure culture from the joints and heart blood. This case made clear several important facts : (1) the early and definite affection of the heart which we had suspected previously to be a result of the infection became now a certainty ; (2) the post-mortem appearances of the heart and the microscopic changes were analogous to those found in rheumatic fever ; (3) again there was no suppuration in the viscera ; and (4) the kidneys showed that the diplococci were present in great numbers. Inoculations were next made from the cultivations upon six blood agar tubes obtained from the foregoing case and were injected into a rabbit in the usual way.

Rabbit No 5. The rabbit developed the following symptoms. Four days after the inoculations the right carpal joint was swollen and the heart was rapid and excited. Other joint swellings followed. The cardiac rhythm became triple and later the action irregular. There were marked dyspnœa and a mitral murmur. Seven days after we heard a pericardial friction sound and diagnosed also pneumonia over the fronts of both lungs. Upon the previous day a great quantity of thick white urine was passed. On the eighth day the rabbit was killed, with the diagnosis of pericarditis, valvulitis, pneumonia, and polyarthritis. At the necropsy the appearance of the thoracic organs was such as is seen in severe rheumatic fever. There were pleurisy with plastic exudation and

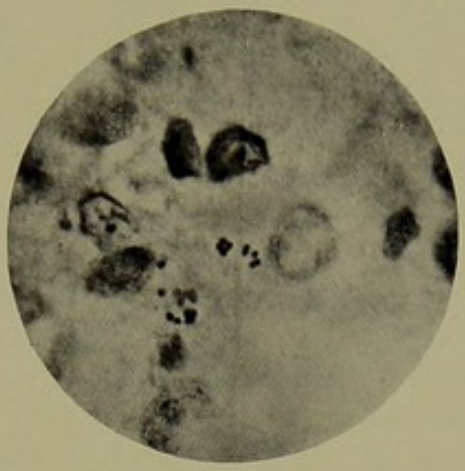


FIG. 18

Microphotograph showing the diplococcus in the mitral valve of a rabbit. × 2100

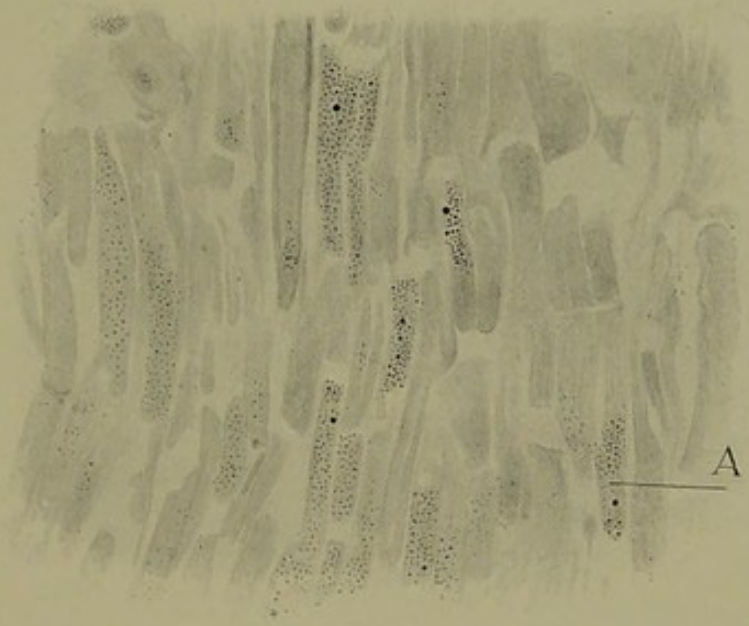


FIG. 19

Section of the myocardium of a rabbit dead from experimental cardiac dilatation, stained with osmic acid to show the fatty changes in the muscular fibres (A).

pneumonia over those parts of the lung that covered the heart. There were also mediastinitis and recent plastic pericarditis with some effusion of clear fluid in the pericardial sac. The heart was greatly dilated and the muscle was pale. The mitral valve showed early endocarditis. The liver was enlarged and mottled red and white, just such an appearance as is seen in acute rheumatism. There were no white firm areas as in former cases. The spleen was enlarged and was softer than in previous cases. Both kidneys were pale. The joints contained an opalescent fluid and the connective tissue around them had the gelatinous appearance suggestive of a nodule formation. The tendon sheaths around the right tarsal joints contained an opaque fluid. There was no peritonitis. The tonsils were not affected. The bladder was much distended and thick white urine was withdrawn by a pipette. This fluid on adding acetic acid cleared rapidly. The urine under the microscope showed numerous dumb-bell shaped crystals of uric acid, diplococci, and granular casts. There was no suppuration in the viscera. The heart muscle was at once teased and examined microscopically. Numerous clear granules were seen in the fibres, which stained faintly with osmic acid. Under microscopical examination the diplococci were demonstrated in the mitral and tricuspid valves and in the pericardium; also in the joints, connective tissue around the joints, kidneys, and liver. In the lungs and pleuræ they were present in very great numbers, especially towards the surface. Bacteriology. The inoculations were made in the usual way and a free growth obtained upon blood agar. The organisms were in this case isolated from the bladder.

Note. This case presented the most striking resemblance to severe rheumatic fever both clinically and in the pathological results. The condition of the thoracic viscera was just as is seen in the virulent pleuro-pericarditis of rheumatic fever in childhood. The diplococci in this case were demonstrated in the lungs and liver.

Case 5. A youth, aged 16 years, was admitted into St. Mary's Hospital on March 20, 1900, suffering from rheumatic pericarditis. This was the second attack of rheumatic fever and in addition he had suffered from chorea at the age of 15 years. The illness had commenced a fortnight previously to admission with a sore throat and pain in the right knee,

followed by shivering, and pain in the chest. On admission there was general pericardial friction and mitral (and a suspicion of aortic) endocarditis. The heart was much dilated and right heart failure was threatened. On this account he was venesected. This patient made an excellent recovery from the pericarditis, but left the hospital in May with evidence of organic valvular disease. Bacteriology. On March 24, the patient was venesected and due precautions were taken to obtain the blood free from contamination. Three different media were used: (1) the milk medium (acid); (2) the pork medium (strongly alkaline); and (3) the bouillon medium (alkaline). Anaerobic tubes were made of these media. In one anaerobic milk tube the strepto-diplococci were growing vigorously. The remaining tubes were sterile. From the anaerobic milk tube sub-cultures were made and a blood agar tube was inoculated upon which discrete colonies of the diplococci made their appearance. Sub-cultures were made and the remainder injected intravenously into a rabbit.

Rabbit No. 6. Four days after inoculation the rabbit limped, the right knee-joint was swollen, and it had lost flesh. Eleven days afterwards it was still limping and was thinner. Twenty-one days afterwards, though the heart was very rapid, the limp had disappeared and a slight improvement set in. Five weeks afterwards there was a relapse and both hind legs became affected, and the animal could not support the weight upon them. It was now very thin. The heart sounds were very feeble and rapid but there was no murmur. This affection of the hind limbs seemed to be a paralytic phenomenon and no swelling of the joints was apparent. There was no twitching. This symptom also passed away in about three weeks and the animal could use both hind legs again in a normal manner.

CASE 6. A girl, aged thirteen and a half years, was admitted nto St. Mary's Hospital on March 25, 1900, suffering from active rheumatism and morbus cordis. In January 1900, the first attack of rheumatism occurred. The present illness had lasted three weeks. On admission the child was very ill. There were numerous nodules, the heart was dilated, there was organic mitral disease, and there was general pericarditis. She grew rapidly worse and died on the 30th. The necropsy, which was made eight hours after death, showed recent lymph

upon the visceral pericardium and turbid fluid in the sac. There were recent granulations upon the mitral valve and some thickening of the cusps of the aortic valve. The liver showed an early nutmeg change. The spleen was firm and dark. The kidneys were pale. The pericardial fluid was definitely acid in reaction. On microscopical examination the heart showed very marked fatty change in the muscle fibres and diplococci were demonstrated in the granulations of the mitral valve. Bacteriology. Films made of the pericardial fluid after incubation showed diplococci and a short bacillus. A cusp of an aortic valve and a piece of the mitral valve were stained and examined in bulk but no organisms were found. A section of the mitral valve showed the cocci in the granulations. The following cultures were made : (*a*) the pericardial fluid was incubated in pipettes ; (*b*) the lymph was introduced into (1) blood agar, (2) the milk medium (acid), and (3) the pork medium (alkaline) ; and (*c*) fragments curetted from the mitral granulations were also placed in the same media. The heart blood was also introduced into other tubes of the same media. Anaerobic tubes were made of the milk medium (acid). The results were as follows. Two of the pipettes of pericardial fluid were sterile, one contained the diplococci, but with them numerous small bacilli, and the odour of the fluid was offensive. The blood agar was sterile. The tube of the heart blood was sterile. A blood agar tube was made from the pericardial fluid. The following inoculations into animals were made. 1. Five minims of the pericardial fluid containing the diplococci and bacilli were injected intravenously but the result was negative. 2. Later the contents of six blood agar tubes from a sub-culture were inoculated but the result was again negative. Later a third attempt was made. The culture upon blood agar was growing, but not vigorously, and a sub-culture was accordingly made in the acid medium and then this re-transferred to six blood agar tubes.

Rabbit No. 7. A rabbit was inoculated but no apparent result followed until three weeks after the inoculation, when a definite systolic murmur was detected at the apex and the temperature in the rectum was found to be 102.8° F. No joint lesion developed and after detecting the murmur each day for a week the animal was killed. The necropsy showed definite tricuspid and mitral endocarditis and a definite excess

of clear fluid in the peritoneal cavity. The organism was demonstrated in the valves and parietal pericardium in which there was definite cellular exudation.

Note. This case corresponded clinically to the well-known rheumatic condition of organic valvular disease occurring without arthritis.

The pyrexia in the rabbits in these cases was moderate, the range being from 101° to 103.4° F. The temperature was taken in the rectum. In the more severe cases the fever was continuous though with some oscillation.

CASE 7. A boy, aged nine years, was admitted into the Hospital for Sick Children, Great Ormond Street, on February 26, 1900, suffering from rheumatic fever from which his mother also had suffered. On admission there were pericarditis and arthritis. The illness was prolonged and after a partial improvement a relapse of carditis occurred and terminated fatally on April 30. At the necropsy, which was made 30 hours after death, the tonsils were found to be large and inflamed. There was consolidation of areas of both lungs. The heart was large and the muscle pale and soft. The pericardium was generally adherent, the adhesions breaking down easily. There were recent granulations upon the mitral and aortic valves and the pulmonary valve showed very early inflammation. The liver, kidneys and spleen showed the usual changes. At the microscopical examination *the important fact was the demonstration of the diplococci in the tissue of a rheumatic nodule.* The nodule was of about the size of a small pea and was situated over the left olecranon. The diplococci were in small clumps in the fibrous tissue. We are not aware that they have been demonstrated before in these structures, which are looked upon as extremely characteristic of rheumatic fever. Bacteriology. The recent granulations on the mitral and aortic valves were curetted and the heart blood taken in a sterilised pipette. Films from the mitral granulations showed a few diplococci. The milk medium and blood agar tubes were used. The milk medium was treated anaerobically, and from the curetted granulations of the mitral valve a growth of strepto-diplococcus was obtained but it was not abundant. The usual blood agar tubes were made but the growth was poor. Intravenous inoculation in a rabbit (No. 8) proved negative.

Case 8. A man, aged 28 years, came into St. Mary's Hospital on June 7, 1900, suffering from a "sore throat." The illness had commenced with general malaise and pains in the limbs and joints. There was a history of a definite attack of rheumatic fever four years before. The throat was injected and the tonsils were in a condition of acute catarrh. The heart was much enlarged and both mitral and aortic valves were incompetent. The enlargement of the heart, the character of the murmurs, and the pulse all pointed to a previous attack of rheumatic carditis and confirmed the history of previous rheumatism. We diagnosed from the history, the appearance of the throat, and the excited action of the heart that the condition was one of rheumatic tonsillitis. A culture was made upon the acid milk medium and the tube incubated aerobically. Minute diplococci were found in a film in association with other micro-organisms. Bacteriology. Twenty-four hours after the culture had been made a film showed that a diplococcus was growing in association with other micro-organisms and blood agar tubes were inoculated from the milk culture. On the 12th blood agar plates were made from these tubes and a diplococcus isolated and transferred to blood agar tubes. The diplococcus resembled morphologically and in its growth that found in the seven preceding cases. On the 14th the contents of six blood agar tubes were injected intravenously into a rabbit.

Rabbit No. 9. On June 15, the respirations were rapid and the action of the heart was excited. On June 16, the heart sounds were loud and the action was very rapid. On June 18, there was suspicion of a systolic apical murmur and of pleurisy. On June 19, a very loud systolic apical murmur was discovered and both pleurisy and pericarditis were suspected. The rabbit died in the night somewhat unexpectedly. At the necropsy the heart was found to be greatly dilated and there was some excess of fluid in the pericardial sac. The mitral valve showed a large vegetation upon the anterior flap and to this a large ante-mortem clot occupying much of the left auricle was firmly adherent. The posterior flap was reddened. The aortic valves were reddened and the aorta close to the valve showed a small patch of aortitis. The tricuspid valve was reddened. The pulmonary valve was apparently normal. There was recent fibrinous exudation in the pleuræ. The lungs were engorged and solid in small

areas, close beneath the pleuræ. There was no trace of suppuration in any of the viscera. Under microscopical examination the diplococci were demonstrated in the vegetation of the mitral valve, in the pericardium, and pleural exudation. Bacteriology. Cultivations were made anerobically in the acid medium from (*a*) the blood and (*b*) the cerebro-spinal fluid from the lateral ventricles. In both instances the diplococci were obtained in pure culture.

Note. This case by the light of the former one is of extreme interest. 1. It demonstrated conclusively that these diplococci when present in the throat of a man the subject of rheumatic fever will, if isolated during an attack of angina faucium, cause non-suppurative valvulitis and pericarditis, when inoculated intravenously into a rabbit. 2. The presence of the micro-organism in the cerebro-spinal fluid is very suggestive when the close association of chorea and rheumatic fever is considered from this point of view.

General Conclusions and Remarks

Concerning the isolation of the diplococci. 1. We have demonstrated these diplococci in eight successive cases of acute rheumatism. 2. They have been present in five cases in pure culture. 3. We have obtained them (*a*) from the blood of living patients suffering from acute rheumatic pericarditis; (*b*) from the pericardial fluid and from the fragments of granulations removed from the valves after death; and (*c*) from the throat of the living patient suffering from rheumatic tonsillitis. 4. We have isolated them and grown them in an acid medium and also upon blood agar. 5. They have also grown in the pericardial fluid, which we proved on those occasions to be acid. 6. They do not thrive on ordinary media. 7. We have isolated them in pure culture from the joint exudation, heart blood, urine from the bladder, and cerebro-spinal fluid of rabbits that had been inoculated with a sufficient dosage.

Concerning the demonstration of the diplococci in the tissues. 1. We have demonstrated them in the cardiac valves, pericardium, and tonsils, and in a nodule in fatal cases of rheumatism. 2. We have demonstrated them in the cardiac valves, pericardium, joint exudation, kidneys, liver, connective

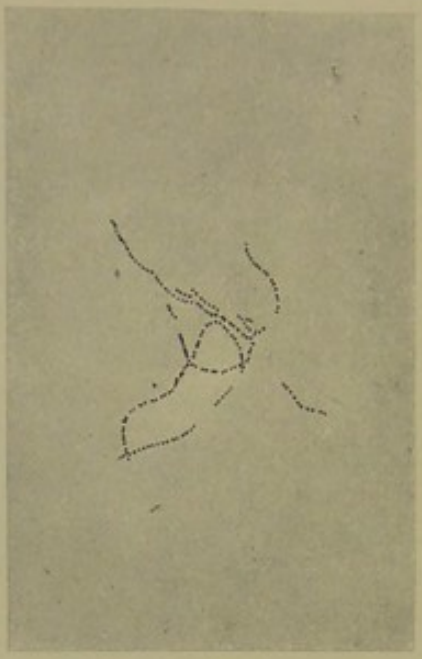


FIG. 20

Film showing the diplococcus in chain form in the incubated pericardial exudation from a case of fatal pericarditis. (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

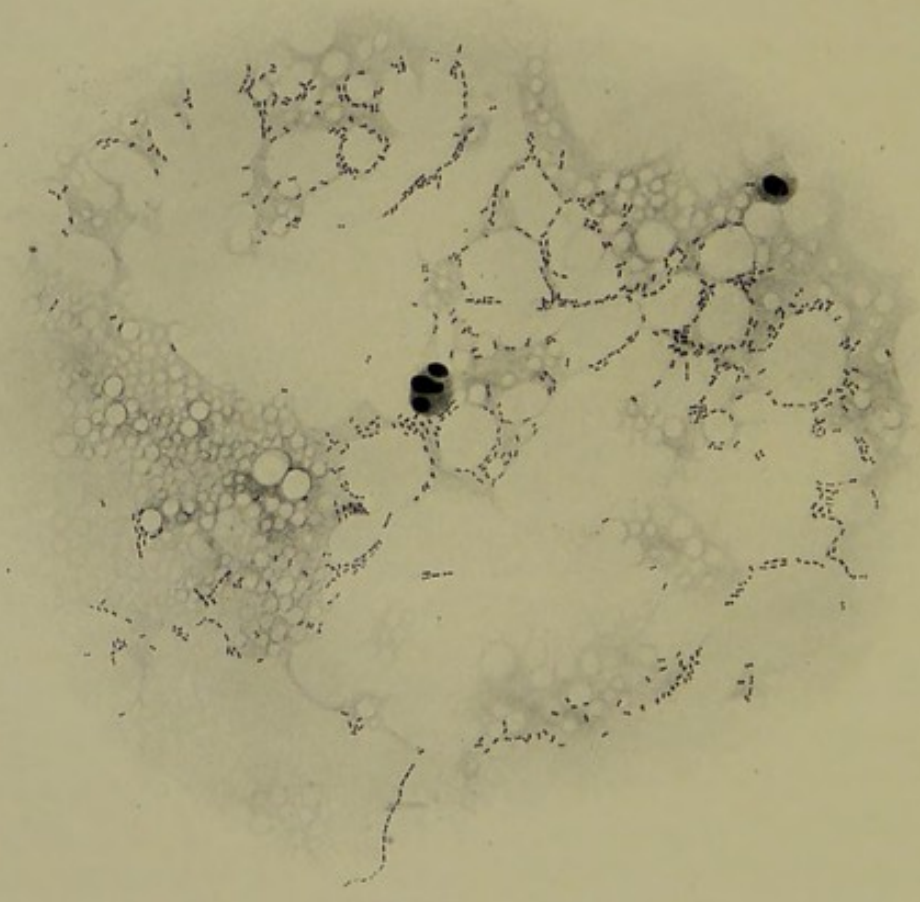


FIG. 21

Film showing the *Diplococcus rheumaticus* growing in the acid-milk medium. (Zeiss, obj. $\frac{1}{12}$, oc. 4.)

tissues, pleuræ, cerebro-spinal fluid, lungs, and urine of rabbits inoculated intravenously.

Concerning the results produced by inoculation of these organisms intravenously into rabbits. 1. They produce a polyarthritis, bursitis, and tenosynovitis. 2. This polyarthritis may completely disappear. 3. In some of the joints that have been affected for a considerable time the fluid is opaque and contains fibrin, endothelial cells, mononuclear and polynuclear leucocytes. In other joints the exudation is clear. 4. In one case they produced a paresis of the lower extremities which passed off in about three weeks. 5. They produce multiple valvulitis and pericarditis, both non-suppurative. 6. They produce in the liver and kidneys a condition of coagulation necrosis. This in the case of the kidneys chiefly occurs in the convoluted tubules. 7. They produce plastic pleurisy and pneumonia. 8. The urine is acid and loaded with urates. 9. They have not produced suppurative foci in the viscera. 10. They produce in the myocardium a condition of fatty degeneration and destruction of the muscle fibres analogous to that found in the human heart as a result of severe rheumatic carditis. 11. The clinical symptoms are characterised by multiple painful joint swellings, wasting, with (in the less severe cases) a maintenance of the appetite. There is moderate pyrexia. 12. The heart is affected early; tachycardia, dyspnœa, and irregularity of cardiac action, together with valvular murmurs, pericardial and pleural friction, have all been observed. 13. The clinical symptoms are, on the whole, remarkably constant when the organism is passed from animal to animal, though the tendency is for increase in the severity of the cardiac lesions and diminution in the arthritis.

I. The Morphology and other Characteristics of the Diplococcus

We are not as yet in a position to state fully the morphological characteristics of this micro-organism. Our research has been concerned more especially with the elucidation of the symptoms and morbid changes that are the result of their access to the living body. We have, however, ascertained the following details.

1. They are micrococci associated in pairs, the individual

elements of which vary somewhat in size but average 0.5 μ in diameter, as measured by Zeiss's micrometer eyepiece.

2. In liquid media they grow in chains of varying length. In solid media they grow in masses that resemble the arrangement of staphylococci.

3. They grow both aerobically and anaerobically. They may be culivated upon ordinary media *but do not thrive and rapidly lose both their virulence and characteristic appearances.* When isolating them from the tissues we have succeeded best with a medium of milk and bouillon slightly acidified with lactic acid, and, on the whole, the anaerobic tubes have proved more suitable to them than the aerobic. When they have been isolated they grow well upon blood agar aerobically at a temperature of 37° C., at which temperature the milk tubes were also incubated. Upon blood agar they form in 24 hours small, raised, yellowish-white, discrete colonies, the average size of which is 0.456 millimetre. The colonies are more or less circular and have, under a high magnification, a slightly granular appearance. By transmitted light they show a darker centre.

4. They stain with the various aniline dyes, though by Gram's method they are easily decolourised.[28] The stain which we have used for them in the tissues and which has given the best result has been carbol-thionin. The metachromatism that is produced with this stain has assisted us in differentiating them from the tissues in which they were lying, for when deeply stained they appear a deep blue, whereas the tissues are usually a light blue or have a red tinge.

II. The Relation of these Diplococci to those Isolated by other Observers

There can, we think, be but little doubt that these diplococci are identical with those discovered by Triboulet in 1897 and by Wassermann in 1899. Triboulet isolated them from the blood in acute rheumatism and grew them anaerobically. He also produced in one instance a valvular lesion in a rabbit but did not produce polyarthritis. In spite of this absence of joint lesions he thought these diplococci were the cause of rheumatism. Wassermann originally isolated them after death from a case of rheumatism and produced polyarthritis and tenosynovitis in a series of rabbits. He grew them best

on a strongly alkaline medium aerobically, but did not apparently obtain any valvular lesions. In addition to the isolated lesion obtained by these observers the entire picture of rheumatic fever resulted in our cases. We have succeeded with acid but failed with strongly alkaline media.

III. Is this Organism the Cause of Rheumatic fever?

In the face of the statements by Achalme, Thiroloix, Bettencourt, Litten, and others, we cannot claim that this diplococcus is the only cause of rheumatic fever. More extended observations will doubtless settle this most important point. That it is one cause we believe to be proved to all practical purposes by this investigation, and we believe it highly probable that it will prove to be the cause of all cases of rheumatic fever which conform to the usual type of the disease, for the disease in man, as we have insisted before, is a very definite one and therefore probably caused by a specific micro-organism.

IV. The Clinical Likeness between Rheumatic Fever and the Disease Produced by the Diplococcus in Rabbits

The resemblance between the disease produced in rabbits and the rheumatic fever of man is, we think, a very striking one. There is moderate pyrexia and wasting, and the occurrence of a painful polyarthritis, which is metastatic and may entirely disappear. The tissues around the joints, such as the tendons and bursæ, are also affected, and the large joints are especially liable to this arthritis. The heart is affected early, even before the joints or irrespectively of the joint affection. In the severe cases there occur pericarditis, endocarditis, pleurisy, and pneumonia, and the myocardium suffers as it does in acute rheumatism. The urine is acid and loaded with urates. There is no suppuration in the viscera and the peritoneum as a rule escapes as it does in rheumatism. In one case following the arthritis there occurred a passing weakness of the hind limbs. We do not venture to explain this, but think it suggestive of paralytic chorea.

The course of the disease is, as in rheumatic fever, prolonged and inclined to recovery unless the dose is a large one. Finally there is a tendency to exacerbations of symptoms similar to

those so frequently observed in the rheumatism of childhood. In this it is well known that even when progress seems to be satisfactory there may be, without assignable cause, a sudden exacerbation of symptoms which may almost as quickly disappear; in the rabbit also these variations may be noticed.

V. The Demonstration of the Diplococcus in the Tissues

The demonstration of these organisms in the human tissues is not easy. We think that one reason for the difficulty lies in the fact that rheumatic fever is essentially a disease to which there is great resistance. Even in fatal cases the reparative processes are often well advanced at the site of some of the local lesions. Such tissues, too, as the granulations upon valves, the nodules, and the pericardial exudation are among the more difficult of the structures that require investigation under the highest powers of the microscope. The micro-organism, again, is a very minute one and often present in compact masses which are liable to be mistaken for Mast-zellen. Their discovery in the rabbit is far easier, for the animal can be killed early in the disease, and it is a point of great interest that numerous diplococci can be demonstrated in the pericardium before any cellular reaction of consequence has had time to develop. The tissues have afforded us the very greatest assistance both in localising the diplococcus and in getting a true picture of its appearance in the viscera.

We are not at present in a position to state with confidence the number of diplococci that are present in the human tissues, but have good reason to believe that at some period of the illness they are present in large numbers. Usually they are seen in small clumps, but when they reach a free surface they are sometimes in large masses, although the individual diplococcus is very small. In the short description that is given below of their occurrence in particular regions, such statements as are made are supported by the proof of microscopic demonstration.

1. *Occurrence in the heart.* The valves of the heart are attacked from within and the diplococci are not at first found upon the surface. In both man and rabbits we have examined valves in a very early stage of the local disease and found the diplococci beneath the endocardium in the substance of the

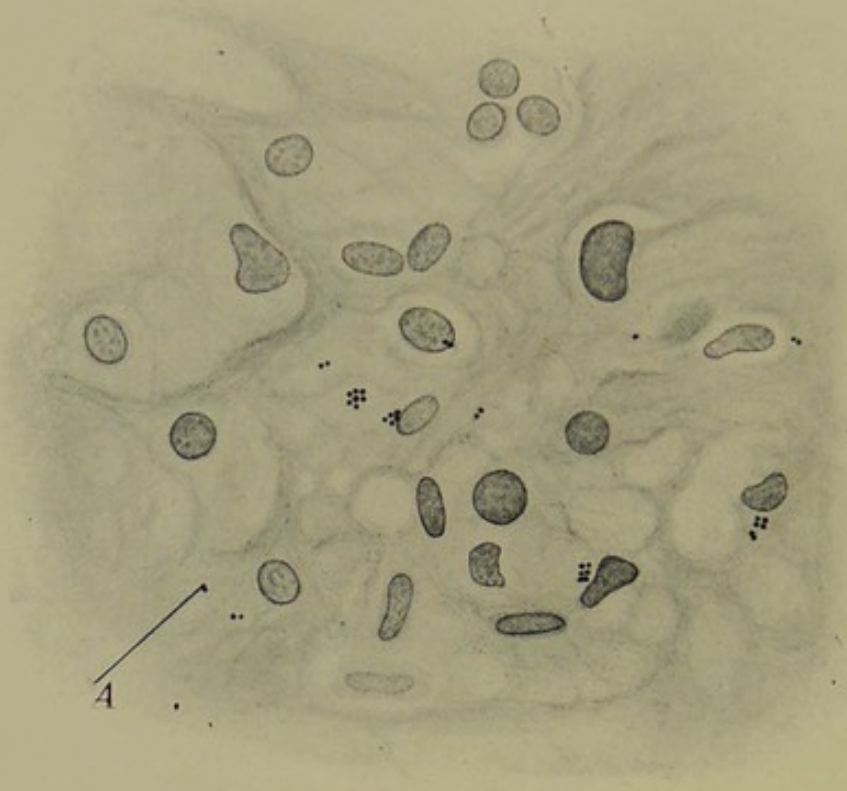


FIG. 22

Section of rheumatic nodule showing diplococci in the tissue. (Zeiss, obj. $\frac{1}{12}$, oc. 3). *A*. A diplococcus.

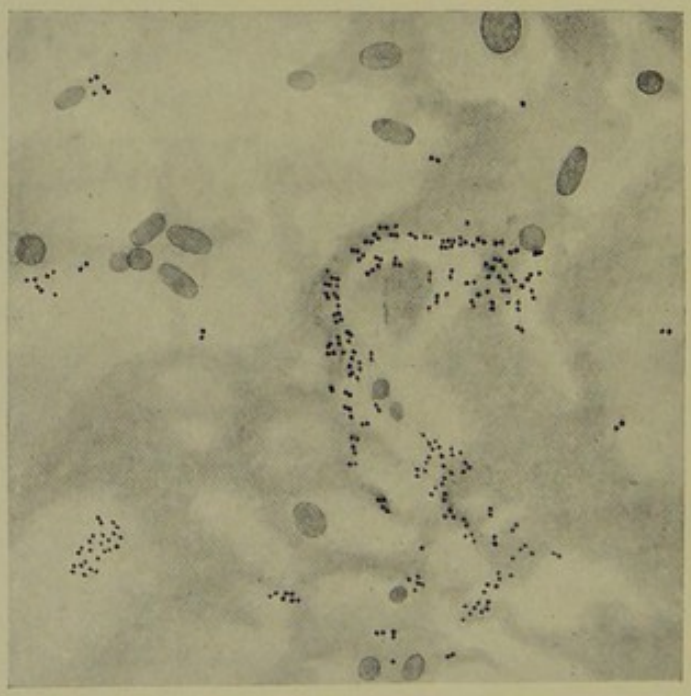


FIG. 23

Section of a subcutaneous nodule in a rabbit produced by intravenous inoculation of the diplococcus. Many of the organisms are seen in the swollen tissues. (Zeiss, oj. $\frac{1}{12}$, oc. 3).

valve and at the base in the region of the valve ring. When the connective-tissue proliferation they produce in the valve becomes a granulation and breaks down then they may be found on the surface; they may also be found in the connective-tissue cells of the valve and chordæ tendineæ. It is especially difficult in our experience to demonstrate them in the necrotic material of an early granulation. They are found in man in the deeper part of the visceral pericardium, in the fibrino-cellular exudation, and in the parietal pericardium. In the rabbit they can be seen in the visceral pericardium and in the parietal pericardium following the course of the blood-vessels. In the heart-wall they are seen sometimes in the areolar tissue near the blood-vessels in the intermuscular septa. In the very earliest stages these organisms can be discovered in these tissues without having apparently caused any reaction, but a proliferation of connective-tissue cells and a free exudation of leucocytes is usually easily recognised as a result of their presence. During the actue phase of rheumatic pericarditis they circulate in the general blood-stream.

2. *Occurrence in the nodule.* The discovery of the diplococci in the rheumatic nodule is, we think, of especial interest, for this lesion above all is looked upon as highly characteristic of rheumatic fever. It is a strong point in favour of the view that these diplococci are the cause of the symptoms of rheumatic fever. Further, it completes the proof of the analogy of this lesion with the valvular and pericardial inflammation—an analogy which has been long suspected by clinicians. In the rabbit the connective tissues near the affected joints are sometimes swollen and gelatinous. In one case a nodule appeared over a vertebral spine and after a month gradually disappeared. Sections of the tissue in this condition show the three zones that are found in the rheumatic nodule. This series of changes in these tissues is a strong support of the views expressed by Dr. Poynton and Dr. Still in the Transactions of the Pathological Society of London for 1899 upon the Structure of the Rheumatic Nodule.

3. *Occurrence in the kidney.* This we believe to be one of the most interesting aspects of the subject and we briefly recapitulate here the chief facts that have come to light. In this first place, there is the definite proof of their occurrence in the kidneys of rabbits after death. They are found especially

in the convoluted tubules lying in the cells and produce coagulation necrosis of the protoplasm. Secondly, their presence is associated with a urine which is acid, contains granular casts, and is loaded with urates. Thirdly, they have been isolated and cultivated from the urine in the bladder of rabbits. Since we ascertained these facts we have had no opportunity of following up the investigation in the human kidney. The indications, however, seem clear. It is highly probable that the kidney takes an important part in the preservation of the organism against the results of this infection. The character of the urine in rheumatic fever, the occasional occurrence of nephritis, possibly, too the occurrence of infarcts, together with the researches of Chvostek and Singer, all point to an investigation on these lines as likely to produce some valuable facts. Have the relapses that occur so frequently any dependence upon the condition of the kidney ? Does the occasional association of gout and rheumatic fever bear any relation to the occurrence of renal lesions ? These, among others, are the problems that suggest themselves to us. Finally, the acute nephritis which sometimes occurs in childhood without any apparent cause may possibly find its solution as being in some instances, the result of this infection.

4. *Occurrence in the liver.* In the rabbit we have found in the liver areas of coagulation necrosis. The liver cells undergo a rapid destruction and the micro-organisms can be demonstrated within them. In this organ they do not stain well and our examination of these sections leads us to suppose that they are destroyed by the agency of the liver cells. As yet we have not found in the liver of the rabbit that extreme vascular engorgement seen in rheumatic fever, but the hepatic venules are more dilated than usual. In one severe case of rheumatic fever we found the condition of the liver cells resembled closely that found in the rabbit, and we believe that in this case also the diplococci, whose presence we had proved by isolating them from the pericardial fluid, were being destroyed in this organ. The small size of the micro-organisms and the fact that they stained with difficulty does not, however, permit as yet a dogmatic statement upon these points.

5. *Occurrence in the joints.* We have no personal knowledge of their occurrence in the joints in the human being, but Triboulet discovered a diplococcus in the joint exudation.

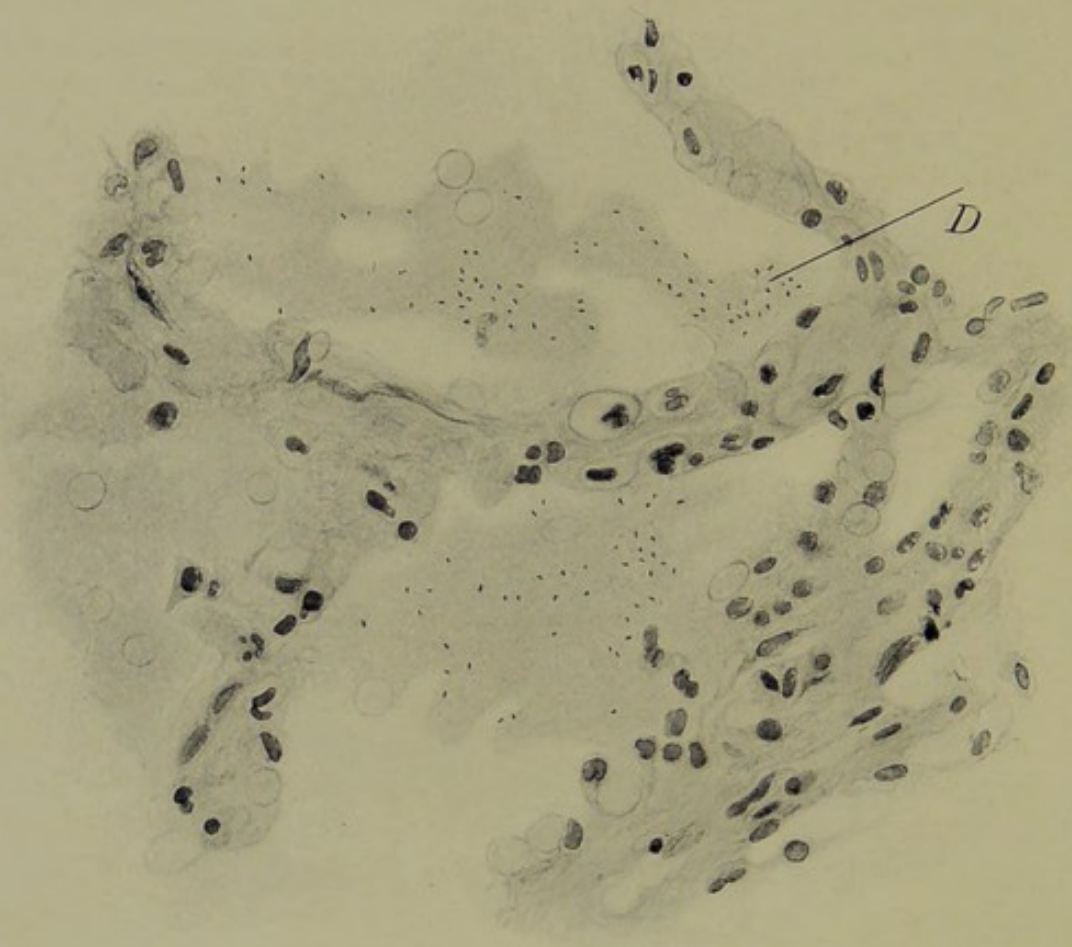


FIG. 24

Section of pulmonary alveoli from a rheumatic pneumonia showing (*D*) diplococci. (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

They occur, sometimes in vast numbers, in the exudation in the rabbit. The fluid in the joints of rabbits may be clear or opaque and may even have the consistence of pericardial lymph. This thick fluid is found in the joints that have been affected for some time and such joints remain distended with this fluid. Possibly this may be thought to be an important difference between the condition produced artificially in rabbits and the rheumatic fever of man. In no single case, however, have we found suppuration in any of the viscera associated with this condition of the joints; further, the exudation is definitely fibrino-cellular in character. We lay especial stress upon this point, for we are sure that to come to the conclusion that this condition found in the rabbit was a suppurative one simply from the macroscopic appearance of the exudation would be an error. The disease must be studied both clinically and pathologically and the affected organs examined microscopically before pronouncing upon the nature of the infection. The bursæ and tendon sheaths are affected in the neighbourhood of the joint in rabbits as in man. As further evidence upon the question of suppuration the following experiment is of value. A rabbit was inoculated under the skin of the abdomen with the contents of six blood agar tubes of a virulent culture. A large firm swelling resulted, a gigantic nodule, which increased in size for some days and then gradually subsided without any indication of abscess formation. There were no symptoms of a constitutional affection and except for this slightly tender swelling no clinical symptoms followed. Apert, in a similar experiment with the diplococcus, isolated by Triboulet and himself, produced a like result.

6. *Occurrence in the lungs and pleuræ.* In the lungs and pleuræ of one of the rabbits that had been killed when suffering from pericarditis, endocarditis, pleurisy, and pneumonia we demonstrated diplococci which we believe to be identical with those found in the other viscera. They were present in masses and in vast numbers beneath the visceral pleura and in the alveoli of the lungs. The alveoli were filled with an exudation resembling very closely that seen in lobar pneumonia, though the exudation had a less reticular arrangement. In a case of rheumatic morbus cordis complicated with pneumonia we have also demonstrated diplococci in the alveoli of the lungs

in great numbers. More than this we are not prepared to state, for the organisms were not isolated in this case, and it cannot therefore, be asserted that they were identical with those which we have found in rheumatic fever. When it is called to mind how frequently both pleurisy and pneumonia occur in rheumatism this demonstration of numerous diplococci in the lungs and pleuræ of the rabbit is suggestive.

7. *Occurrence in the throat.* This, again, is of considerable interest and some of the facts that have come to light have a close bearing upon the treatment of the disease. We briefly recapitulate here the most important of the results. In the first place we have in one case found after death both tonsils large and inflamed and this when the illness had been one of long duration. Before death there had been an exacerbation of rheumatism and this development of tonsillitis is known to occur not only at the commencement but also during the course of a prolonged rheumatic attack. In a film from the deeper part of these tonsils we found diplococci and they were also present in the sections that were made of the tonsils. Secondly, in none of the rabbits, all of which were injected intravenously, was there any inflammation of the tonsils. Lastly, we isolated diplococci from the throat of an adult the subject of rheumatic fever who was suffering from an acute faucial catarrh. These micro-organisms rapidly produced death in a rabbit. After death endocarditis, pericarditis, and cardiac dilatation were found and the organisms once more isolated. It has been already stated that many observers have insisted upon the throat as an important site of infection in rheumatic fever, and these facts strongly support this view. Further, they point to a very watchful regard for the throat in rheumatic patients and to the assiduous treatment of it, not only in the acute stage at the commencement of the illness, but also throughout the period during which active manifestations of rheumatism, other than angina faucium, are present.

8. *Occurrence in the brain and its membranes.* Our facts with regard to this are scanty, but coupled with the observations of Dana, Apert, Westphal, Wassermann, and Malkoff seem worthy of record. In one rabbit after the subsidence of arthritis a paresis of the hind limbs ensued which lasted for three weeks. This was one of our earlier cases and at the time we hardly grasped the significance of the symptom.

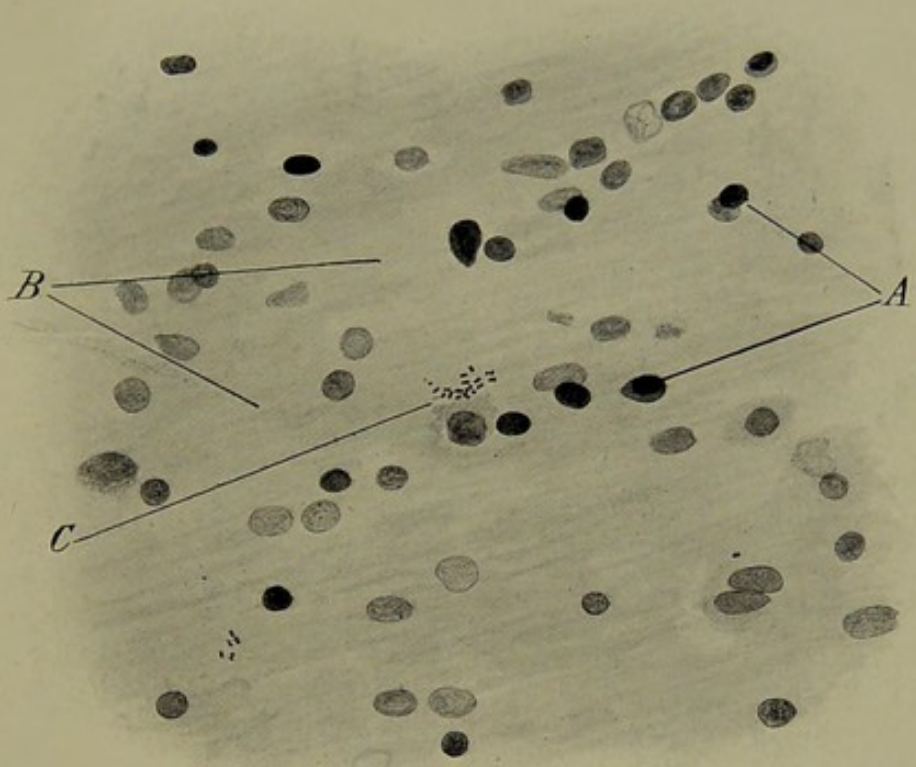


FIG. 25

Film of pleural exudation from a rheumatic pleurisy showing the diplococci. (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

A. Inflammatory cells.
B. Fibrinous exudate.
C. Micrococci.

From another rabbit which died from severe endocarditis we isolated the diplococcus in pure culture from the fluid in the lateral ventricles. In a case of chorea that died in St. Mary's Hospital in 1898 in which the movements were very severe and the heart but little affected we demonstrated numerous diplococci in the perivascular lymph spaces of the pia mater, in its capillaries, and also in some parts of the motor area of the brain. In a case of chorea of similar type we demonstrated them in large number in the mitral valve. In neither case, however, were these micro-organisms isolated. Diplococci have also been discovered in chorea by Dana, Apert, and Wassermann, and in Westphal's case, examined by Wassermann, polyarthritis was produced in rabbits. It is probable, then, that there is a close association between rheumatic chorea and the occurrence of diplococci in the brain and its membranes. It is also probable that the frequency of the occurrence of chorea in childhood depends upon the more extensive dissemination of these micro-organisms in the young, as pointed to by the clinical manifestations of the disease at this age.

VI. The Relation of Infective to Rheumatic Endocarditis

It is clear that the term "infective endocarditis," which has for some time been under suspicion, can now no longer be used in contradistinction to "rheumatic endocarditis," for both are plainly infective. The relation of this type of heart disease to that found in rheumatism has, we believe, been made much clearer by this investigation. That "malignant endocarditis," as we prefer to name it, is due to various causes is beyond doubt, but the frequent association of this type with rheumatism has hardly, we think, received a sufficiently minute investigation. It is indeed thoroughly recognised, but the explanation of its occurrence as due to a mixed infection has possibly been too willingly accepted.

There are cases which have the history and many of the symptoms of rheumatic fever but differ in the progressive nature of the valvulitis and in the occurrence of marked pyrexia, frequent infarction, and nephritis. With such there may be no suppuration. These cases suggest that under

certain circumstances rheumatism may depart from its usual type and yet the infection be still rheumatic—a view which is also maintained by Professor Litten of Berlin.

We can offer no complete explanation of this alteration in the type of the disease, but think that a clue may be found in the distribution and behaviour of the diplococci in the cardiac valves. In simple rheumatism they are not found at first upon the surface of the valve, and the disease tending, as it does, to recovery, they are destroyed by phagocytosis, and possibly in other ways, the valve itself undergoing sclerosis. In the malignant type they reach the free surface and then appear to multiply with great rapidity, for they are found in large masses. If then they are detached by the force of the blood-stream they may possibly give rise to a condition of rheumatic septicæmia recognised clinically as malignant endocarditis. Why they should overstep the barrier of the endocardium in this way we do not know, but it is suggestive that the valves have usually been already injured by a previous rheumatic attack and that the patient is usually in feeble health at the time of the final infection.

Finally, we must say that throughout this investigation we have on all sides received the greatest help. To Mr. H. G. Plimmer we are indebted for assistance, criticism, and advice, and we can only express our obligation by claiming to be his pupils. The physicians at St. Mary's Hospital and the Hospital for Sick Children, Great Ormond Street, have placed their clinical cases at our disposal, and to Dr. H. Thursfield, the registrar at the Children's Hospital, we are indebted for leave to make use of any necropsies that might be of service. To Forbes Tulloch, a student of St. Mary's Hospital, we are indebted for the photo-micrographs. This generous help has greatly lightened the labour of this investigation and has been an additional incentive to pursue the subject.

REFERENCES

[1] *Deutsche Medicinische Wochenschrift*, No. 46, p. 809.

[2] "Ætiology of Acute Rheumatism," *Correspondenzblatt fur Schweizer Aerzte*, 1892, vol. xxii.

[3] *La Semaine Médicale*, 1892, No. 7, p. 48.

[4] "Experimental Bacillary Suppurative Polyarthritis," *Centralblatt fur Bacteriologie*, 1895, Band XIV, p. 269.

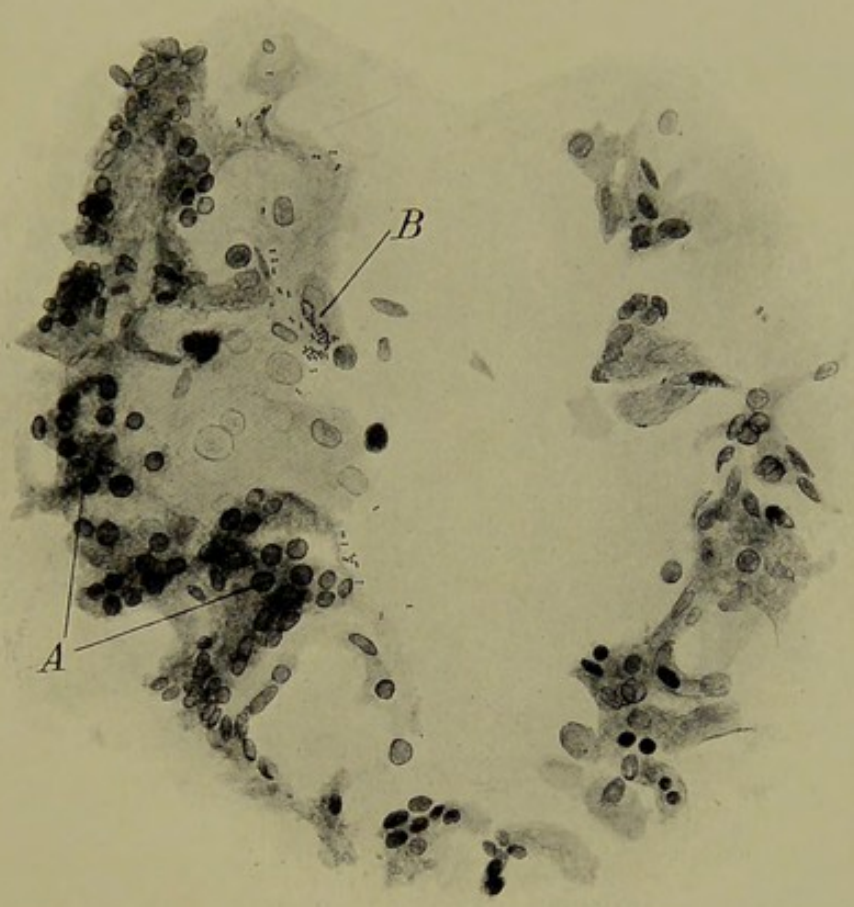


FIG. 26

Section through crypt of tonsil from a case of rheumatic tonsillitis showing diplococci. (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

A. Lymphoid cells.
B. Diplococci.

[5] "Infections from the Pyogenic Micro-organisms," *Riforma Médica*, 1894, Nos. 67 to 68.

[6] *Verhandlungen des Congresses für Innere Medicin*, 1897, p. 99.

[7] *Wiener Klinische Wochenschrift*, 1894, No. 26, p. 449.

[8] "The Microbic Origin of Chorea," *American Journal of Medical Science*, 1894, p. 31.

[9] *La Semaine Médicale*, 1894, p. 376.

[10] "The Role of the Staphylococcus in Acute Articular Rheumatism," *Archives Générales de Médecine*, 1894, p. 513.

[11] *Pathology*, 1896.

[12] *Deutsches Archiv für Klinische Medicin*, 1894, vol. liv, p. 1, "The Bacteriology of Acute Rheumatism."

[13] *Clinical Medicine*, vol. ii, p. 466.

[14] *Lancet*, December 11, 1880, p. 933.

[15] "Harveian Lectures on the Rheumatism of Childhood," 1888.

[16] *Comptes Rendus de la Société de Biologie*, 1891.

[17] "Sur le Rhumatisme Articulaire Aigu," *Annales de l'Institut Pasteur*, 1897.

[18] "The Results of Inoculation of a Bacillus obtained from a Patient with Rheumatic Fever," *La Semaine Médicale*, 1896, p. 376; "The Microbe of Rheumatic Fever," *ibid.* p. 420; "The Bacteriological Examination of the Blood in Two Patients with Rheumatic Fever," *Comptes Rendus de la Société de Biologie*, 1896, p. 268; "A Bacteriological Study of One Case of Rheumatic Fever," *ibid.*, No. 30, p. 882; "The Bacteriology of Rheumatic Fever," *ibid.*, No. 34, p. 945.

[19] *Comptes Rendus de la Société de Biologie*, 1898, Tome V, p. 214.

[20] *Bulletin et Mémoire de la Société Médicale des Hopitaux*, 1898, p. 93.

[21] *Centralblatt für Innere Medicin*, 1897, Band XVIII, p. 825.

[22] *Comptes Rendus de la Société de Biologie*, 1898, Band V, p. 128.

[23] *Archives de Médecine*, Tome II, No. 298.

[24] *Aetiologie und Klinik des Acuten Gelenkrheumatismus.*

[25] "Angina in Acute Rheumatism," *Münchener Medicinische Wochenschrift*, 1899, p. 28.

[26] *Berliner Klinische Wochenschrift*, 1899, No. 29, p. 638.

[27] *Ueber die Maligne (Nichtseptische) Form der Endocarditis Rheumatica, Berliner Klinische Wochenschrift*, 1899, No. 29, p. 644.

[28] This sentence was badly expressed. We intended to convey the fact that the micrococcus did stain by Gram's method, but did not retain the colour firmly.

PAPER NO. IX

THE PATHOGENESIS OF RHEUMATIC FEVER

(Reprinted from the *Transactions of the Pathological Society of London*, 1901)

The first part of the original paper detailed for the purposes of practical demonstration the experimental results we had recorded in the preceding one. This has been omitted and only the part dealing with new facts is published. These consist of an addition to the number of cases examined, an account of some further investigations with the diplococcus isolated from the tonsils of a case of rheumatic sore throat, and a preliminary note upon a rabbit that had shown choreiform movements as a result of inoculation. Lastly, an explanation is given of some of the difficulties met with in the demonstration of the diplococcus in the tissues.

SINCE the completion of the preceding paper, we have obtained further experimental results from the case of angina faucium recorded there (*vide* p. 107). The organisms, isolated from the blood and cerebro-spinal fluid of the rabbit that had developed rheumatism as a result of inoculation from this case, were grown in the usual way, and the cultures from six tubes injected intravenously into a second rabbit. Three days after inoculation the hind limbs became stiff and tender; there was wasting, and marked increase in the rate of the heart's action. Then a systolic murmur developed, and the knee-joints became swollen and tense with fluid. This marked effusion persisted for a week, then gradually diminished, and at the end of three weeks had disappeared. The murmur, which soon vanished, never reappeared, and eventually the animal made a complete recovery. Thus it will be seen this second rabbit passed through an illness characterised by polyarthritis, with possibly also endocarditis.

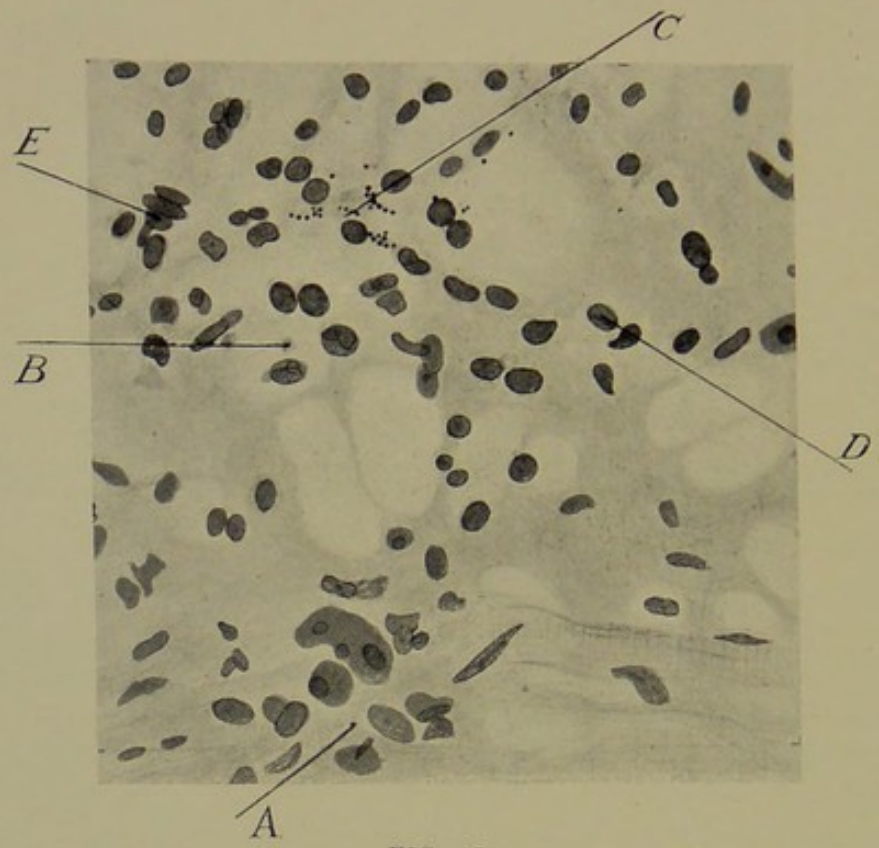


FIG. 27

Visceral pericardium, rheumatic pericarditis (man). (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

A. Cardiac muscle.
B. Visceral pericardium.
C. Diplococci.
D and *E*. Inflammatory cells.

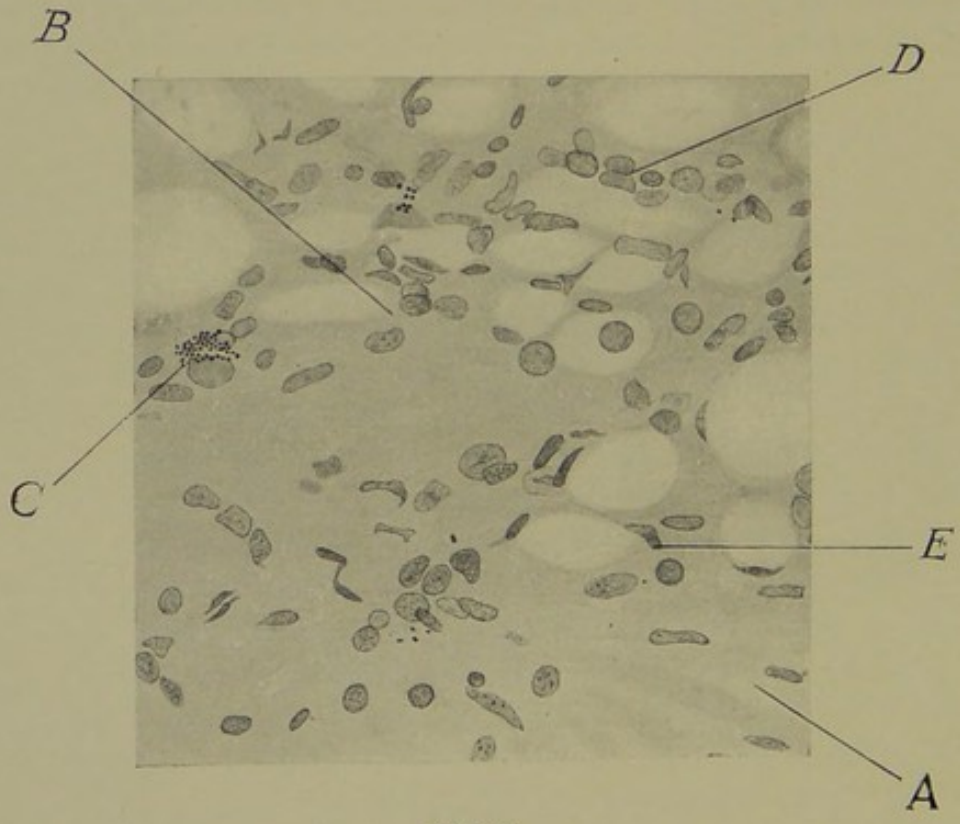


FIG. 28

The visceral pericardium of a rabbit acutely inflamed as the result of the intravenous inoculation with the diplococcus. (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

A. Cardiac muscle.
B. Visceral pericardium.
C. Diplococci.
D. Inflammatory cells.
E. Connective-tissue cells.

Compare Fig. 27.

We have also increased from eight to eleven the number of cases of rheumatic fever in which we have detected the diplococci. Two of these were not favourable for further investigation. The first, an adult, died during the hot summer weather, and all the cultures were contaminated with *B. proteus vulgaris.* We obtained the diplococci, though contaminated in this way, from the bladder after death. The second, a child, was a chronic case with recent valvulitis, and the growth in this case, as in a previous case of the same nature, was feeble. Our experience with cultures from the valves has so far pointed to the difficulty of obtaining a satisfactory growth from them. Cases that are characterised by severe pericarditis are, we have found, those most favourable for experimental results.

The third case, a child, the subject of repeated attacks of rheumatism, was admitted to St. Mary's extremely ill with severe general pericarditis. Upon two occasions the urine was obtained with strict precautions, and mixed with the acid medium. Upon the second occasion a pure growth of the diplococci was obtained and sub-cultured upon blood agar, and the cultures from four tubes injected intravenously into a young rabbit. Three days after inoculation the heart was acting extremely rapidly, and we felt sure there must be pericarditis. The joints were not affected. Then followed slight improvement, but nine days after inoculation there was very definite pericardial friction and considerable wasting. This friction lasted for two days, the heart became feebler, the sounds spaced, the action finally irregular, and death occurred upon the twentieth day from cardiac failure. One joint, the right knee-joint, became affected during the last ten days. The necropsy showed excess of pericardial fluid, with an organising exudate adherent to the visceral pericardium, and also recent mitral and aortic valvulitis. It is of interest that we had never detected an endocardial murmur. The right knee-joint contained an opaque oily fluid ; the lungs showed some basal congestion. The spleen was firm and not enlarged ; the liver dark ; there was no suppuration. The left kidney was very large, and we thought that some remarkable complication had occurred, but this proved to be due to the congenital absence of the right kidney.

The film made from the pericardial exudate (which was shown

under the microscope) has, we believe, cleared up one of the most important of the minor difficulties of this research—one which, perhaps, can only forcibly appeal to those who have closely investigated the microscopy of acute rheumatism. The detection of the diplococcus in the human tissues is difficult, and especially difficult in the valves. Before we discovered them we had repeatedly seen solitary cocci, both in the pericardium and inflamed valves. Later we also found that if the diplococcus is grown upon an unsuitable medium, larger solitary cocci will make their appearance.

Finally, in this pericardial exudate, which had commenced to organise, for it was firm and distinctly adherent, we found a few diplococci, and a considerable number of these larger solitary forms.

The inference is, we think, that this is a peculiar condition of these organisms, probably dependent upon some alteration, either in their virulence, or in the chemistry of the tissues in which they are located, or upon both factors. How much latent energy they possess while in this form, and how long they may persist in the tissues, we are unable to say, though from the point of view of relapses of rheumatism these seem important considerations. If, too, these larger, solitary cocci and this disappearance of the diplococcal forms are evidences of subsidence of the local infection, it is probable that a great local activity of the infection will be evidenced by the converse—a great increase in the number of diplococci, and diminution in their size.

The last experimental result to which we make reference is important, because the rabbit manifested for three days the signs of chorea. We mentioned previously a paresis of the hind limbs as a result of inoculation, but in this case there were sudden involuntary clonic movements of the limbs, and marked facial twitching. The animal was extremely nervous, starting at any sudden sound, and the condition at once forcibly recalled the well-known characters of rheumatic chorea. Six tubes of a culture upon blood-agar had been injected intra-venously, and the symptoms developed upon the fourth day. In addition there was a mitral systolic murmur. We killed the animal and demonstrated the valvulitis, but we have not as yet investigated the brain further than to say there was no meningitis. To recapitulate :

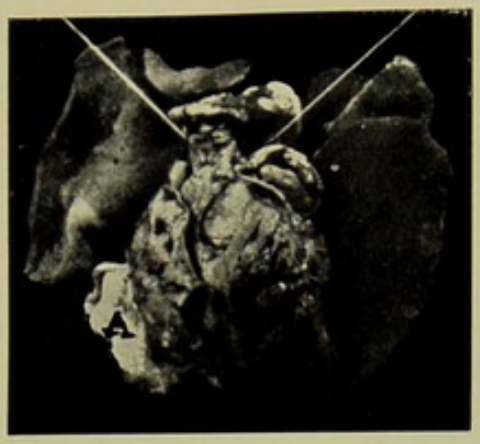


FIG. 29

The heart and lungs of a rabbit showing fibrino-plastic pericarditis, the result of infection with the *Diplococcus rheumaticus*.

FIG. 30

Film of pericardial exudation, rheumatic carditis, showing the diplococci. (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

A. Inflammatory cell.
B. Mass of diplococci.
C. Fibrinous exudate.

We have increased the number of our observations upon successive cases of acute rheumatism from eight to eleven, and have isolated the diplococcus from the urine during an attack of acute pericarditis. We have also produced choreiform movements in a rabbit as a result of intravenous inoculation and traced the appearance of monococcal forms of the diplococcus in a healing *lesion* in the tissues.

Finally, it appears to us from these investigations that rheumatic fever is a disease characterised by great local resistance. The diplococci at the sites of the local lesions are rapidly destroyed. Possibly in this fact lies in part the explanation of the fugitive character of many of the symptoms of rheumatic fever, and the difficulty of finding the organisms in the tissues.

PAPER NO. X

THE INFECTIVITY OF ACUTE RHEUMATISM, WITH ESPECIAL REFERENCE TO CHRONIC ARTHRITIS AND RENAL DISEASE

(Reprinted from the *Clinical Journal* May 1901)

This paper was read at a discussion held by the Chelsea Medical Society in 1901, *an occasion of some interest because it was the first time in this country that the term "acute infective rheumatism" was used as an official title. To some extent it was a résumé of the previous results, and only the new points which were touched upon are given here. These were the occurrence of rheumatoid and osteo-arthritic changes in the experimental arthritis and the possible importance of the experimental renal lesions in directing attention to renal disease in rheumatism.*

We wish to bring forward some further investigations that appear to us to throw light upon chronic arthritis and renal disease in rheumatism.

We have repeatedly demonstrated the diplococcus in the joint exudation in rabbits, and have also found them in the joints in human rheumatism. The organisms are rapidly taken up by endothelial cells and polynuclear leucocytes in these situations, and this may well account for the difficulty of demonstrating them in acute rheumatic arthritis, which is usually of less severe type than that produced experimentally in the rabbit. The presence of the organisms in this form of arthritis brings acute rheumatic affections of joints into line with arthritis, the result of septic, gonorrhœal, and pneumonococcal infections—according to the researches of Drs. Bannatyne, Wohlmann, and Blaxall, rheumatoid arthritis must be included in this group also. Gouty and syphilitic arthritis remain as examples in which no micro-organism has been demonstrated, the former, perhaps, not being the result of a

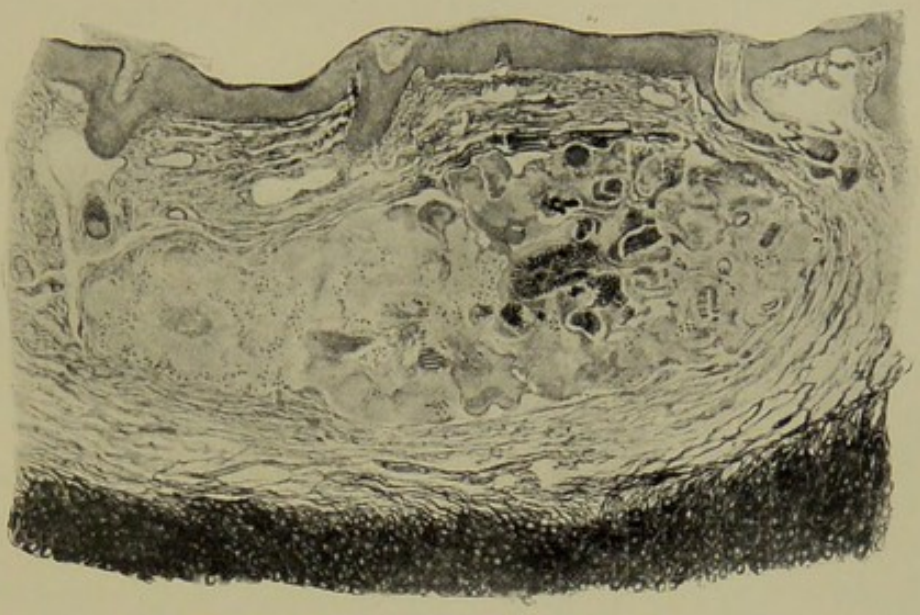


FIG. 31

Section of a gouty tophus under a low power. A stellate mass of biurate of soda crystals is seen in the centre of the nodule surrounded by necrotic tissue.

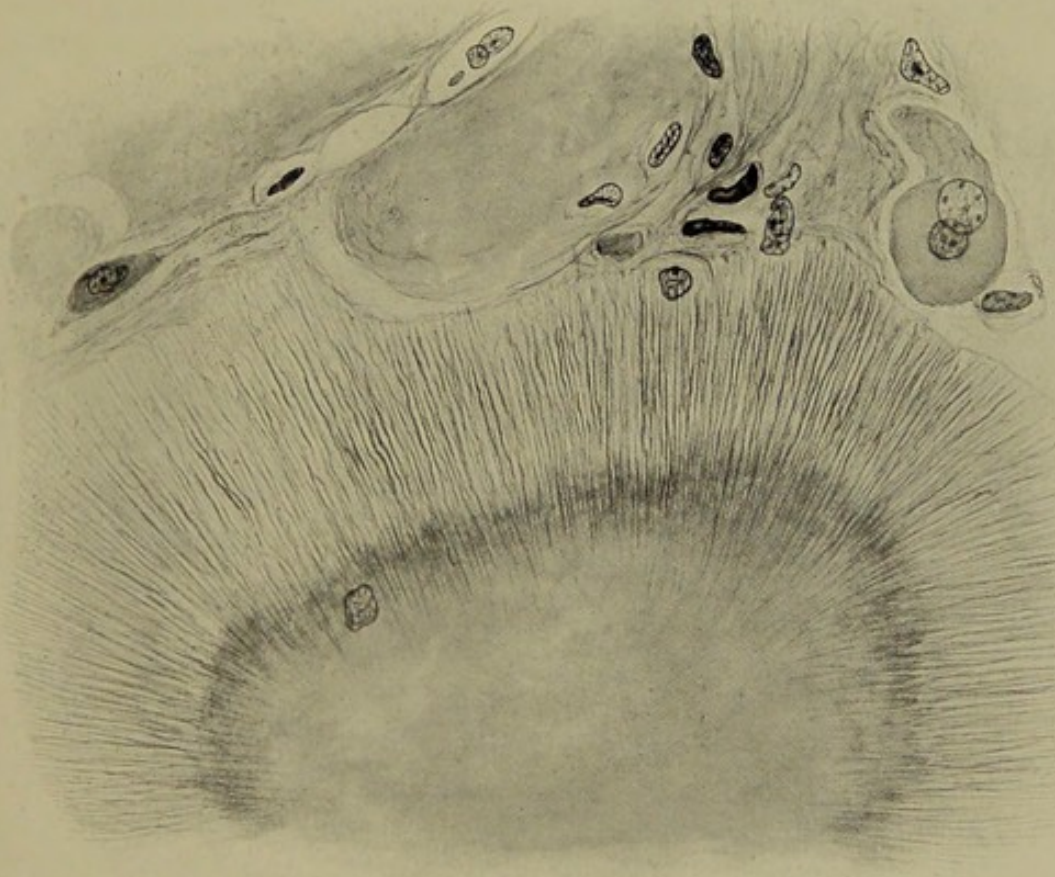


FIG. 32

Section of the same tophus under high magnification (Zeiss, obj. $\frac{1}{12}$, oc. 3), showing peripheral striation of the necrotic tissue in which there is biurate of soda. The appearance strongly suggested a local origin of the biurate of soda in the damaged tissue.

microbic infection, the latter almost certainly being micro-organic.

In our previous investigations a joint in one of the rabbits that developed polyarthritis remained in a chronic state of inflammation, and did not subside. In every other instance the swellings either completely subsided, or the animal died from the infection ; but in this case, though the animal recovered except for some slight valvular disease, the left shoulder-joint remained swollen and slightly tender from May 30 until October 8, when the animal was killed. Then we found much gelatinous swelling of the connective tissues around the joint, with thickening of the capsule and erosion of the cartilages. This result suggests that researches in this direction may eventually throw light upon the more chronic forms of rheumatic arthritis.

Another point to which we wish to call attention is the condition of the kidneys in acute rheumatism. In fatal cases we have found very definite changes in the parenchyma, especially of the convoluted tubules. There is marked cloudy swelling of the protoplasm of the renal cells with fatty change, and some desquamation. The change is diffuse—that is, it affects a great number of the convoluted tubules. Further, we have isolated the diplococcus from the urine in acute rheumatic pericarditis, and recently we have isolated it from the kidney and urine in the bladder after death.

In rabbits the kidneys are more severely affected, but the changes are of the same type ; there is much cloudy swelling and also some desquamation of the renal cells, and in their kidneys we have repeatedly demonstrated the micro-organisms. Further, in the rabbit we have traced this condition step by step to the formation of a white infarct, which certainly in this animal, and most probably in man, is *not* always the result of a gross embolism, but of the invasion of a particular area by a considerable number of the diplococci. As a result the cloudy swelling in that area passes into the stage of necrosis, and thus is produced the white infarct.

It appears to us that the kidney is an important site for elimination of the poisons produced by the rheumatic infection, and that in this process the kidney itself suffers to some extent. Usually the injury is not gross, for though albuminuria, and

in some malignant cases hæmaturia and nephritis occur in this disease, as a rule there is not albuminuria or evidence of serious renal inflammation.

When a white infarct heals, we know the result is a scar, and it is possible that repeated attacks of acute rheumatism may do permanent damage to the renal tubules, not of the gross nature found in the infarct, but of a grade sufficient in severity to destroy the functions of many tubules, and perhaps lead to the gradual replacement by fibrous tissue. In brief, repeated attacks of acute rheumatism in the young may lead to fibrosis of the kidney in the adult, or, short of that, impair the function of the kidney for the elimination of the rheumatic poison in later life. As a result of this it may be that a subsequent attack of rheumatism in adult life—though less severe, because the adult is less susceptible—is more chronic, because the poisons are eliminated with more difficulty.

When we turn to gout we know that the kidneys suffer much in the disease, and that some authorities give to the kidneys the first place in its causation, and all allow the impairment of their function as a prominent factor in the more chronic, inveterate, and cachectic types.

For these reasons it seems to us important to study the kidneys very closely in acute rheumatism, and perhaps it may be found that albuminuria is more frequent than is generally supposed, or that the peculiar condition of cyclical albuminuria may sometimes be a result of the impairment rather than destruction of function that appears to be the result of rheumatic fever.

The last point we touch upon is concerned with malignant endocarditis. We have now collected many facts to show that some of these cases are truly rheumatic, and not the result of secondary infections.

This suggests by analogy that some of these lesions of joints that run on to ulceration and destruction of cartilage may be really rheumatic. The disease has there altered in type, and for some reason has become locally malignant in these situations, as it sometimes becomes in the valves. This we should say is not a new suggestion, but is commented upon in the classical work upon pathology by Wilks and Moxon and clearly deserves fresh consideration.

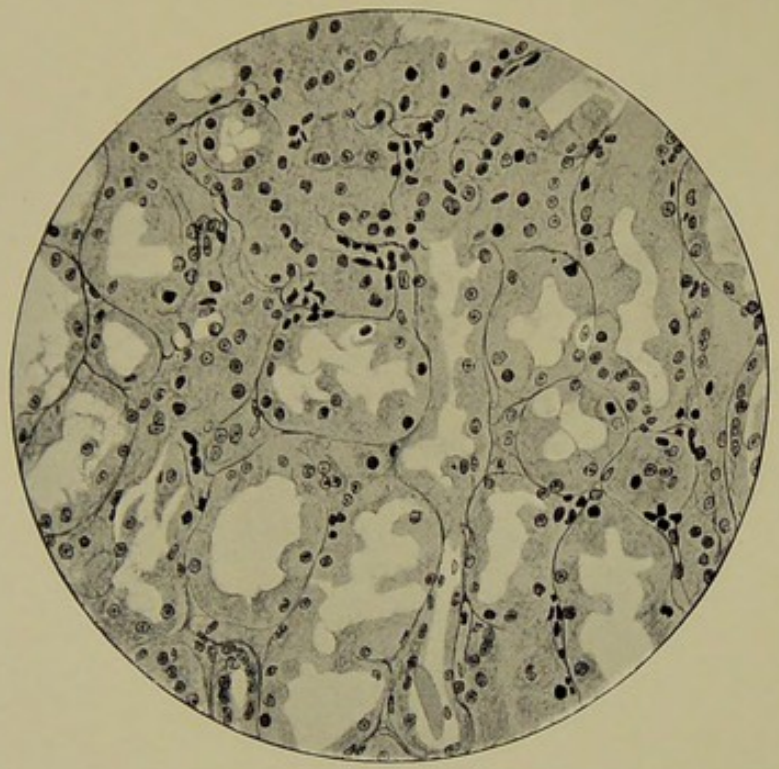


FIG. 33

Human kidney. Fatal acute rheumatism: Section through convoluted tubules showing cloudy swelling, necrosis and desquamation of the epithelium.

FIG. 34

Kidney of a rabbit dead of experimental rheumatism. Section showing diplococci, cell-necrosis, and desquamation of the epithelium in the convoluted tubules. (Zeiss, obj. $\frac{1}{12}$, oc. 2.)

A. Tubule.
B. Coagulative necrosis.
C. Desquamation.
D. Diplococci.

PART II

SUB-GROUP B

THREE PAPERS UPON ARTHRITIS

XI. OBSERVATIONS UPON THE ARTHRITIS PRODUCED IN RABBITS BY THE INTRAVENOUS INOCULATION OF A DIPLOCOCCUS ISOLATED FROM CASES OF RHEUMATIC FEVER

XII. AN EXPERIMENTAL PRODUCTION OF THE OSTEO-ARTHRITIC TYPE OF RHEUMATOID ARTHRITIS

XIII. OBSERVATIONS UPON CERTAIN FORMS OF ARTHRITIS

PAPER NO. XI

OBSERVATIONS UPON THE ARTHRITIS PRODUCED BY THE INTRAVENOUS INOCULATION OF A DIPLOCOCCUS ISOLATED FROM CASES OF RHEUMATIC FEVER

(Reprinted from the *Transactions of the Pathological Society of London* 1901)

We had two objects in view when writing this paper. The first was to demonstrate more fully and decisively than we had heretofore the constancy and reality of the arthritis produced by the diplococcus. The advisability of this step has been justified by subsequent experience, for the repeated failures of some other investigators to produce any experimental lesions with this micrococcus would have otherwise made us almost fear that the idea might arise that we had drawn on our imaginations in the descriptions of our results. The second object was to place on a scientific basis the investigation of non-suppurative arthritis of the rheumatic and rheumatoid types. A possibility only to be realised when the ability to obtain such lesions by intravenous inoculation *was obtained. Lastly, in this paper we gave our reasons for the choice of the name "diplococcus rheumaticus."*

We propose, in the present communication, to demonstrate the nature of the arthritis which is produced by the intravenous inoculation into rabbits of a diplococcus which we have isolated from eighteen cases of rheumatic fever.

The number of clinical cases that we have investigated, the constancy of the experimental results, and the explanation they afford of the phenomena of the disease, appeal to us as evidence sufficiently strong to warrant the name *Diplococcus rheumaticus* being applied to this organism.

Guided by these facts, we turn now to the study of the experimental arthritis. We find that it is a prominent symptom

in the disease that is produced, but it is not invariable. For some months after our first investigations we failed to observe the occurrence, but latterly we have again met with a considerable number of examples. It must not be thought that at the time we failed to observe arthritis our results were negative ; on the contrary, pericarditis, valvular disease, or both, occurred with remarkable constancy. In its varied manifestations the disease produced in rabbits resembles the rheumatic fever of childhood rather than that of the adult. But the arthritis is more severe, and, without losing sight of the distinction, between a serous and synovial membrane, we would compare it, in its severity, to the pericarditis of childhood.

Thus in rabbits we have found clear or slightly blood-stained effusions, comparable to the early exudations in acute pericarditis, and then, again, opaque exudations with flakes and fibrino-cellular exudation, such as are so frequently seen in the rheumatic pericarditis of childhood.

These conditions, we are aware, are not unknown in man, to quote from the classical work on pathological anatomy by Wilks and Moxon. Upon this subject of rheumatic arthritis they write, " Sometimes you find the joint much distended with turbid fluid, and its surface pink from congestion of the vessels. In other cases large flakes of lymph float in the fluid, or a coating of lymph is found lining the whole of the synovial surface of the joint. . . . Again, it is not only within the joints that you see evidence of inflammatory action in rheumatism, but also in the sheaths of the tendons. We have several times found the sheaths of the extensors, where passing the wrists, full of the same turbid flaky fluid as was present in the wrist-joints."

In rabbits, also, tenosynovitis and bursitis may be observed, as well as arthritis.

Usually several joints, and these the larger ones, are affected. The third day is the most usual time for the first indication to be seen of arthritis, but a week or longer may elapse, and the date of the various joint infections may be separated by an interval of some days. The acute arthritis is painful, the swelling may be slight, or the joints distended with fluid. Recovery may be complete, but in two cases one joint remained swollen for some months. When the animals were killed we found thickening of the fibrous tissues of the joints, and a tenacious fluid resembling unboiled white of egg. We have

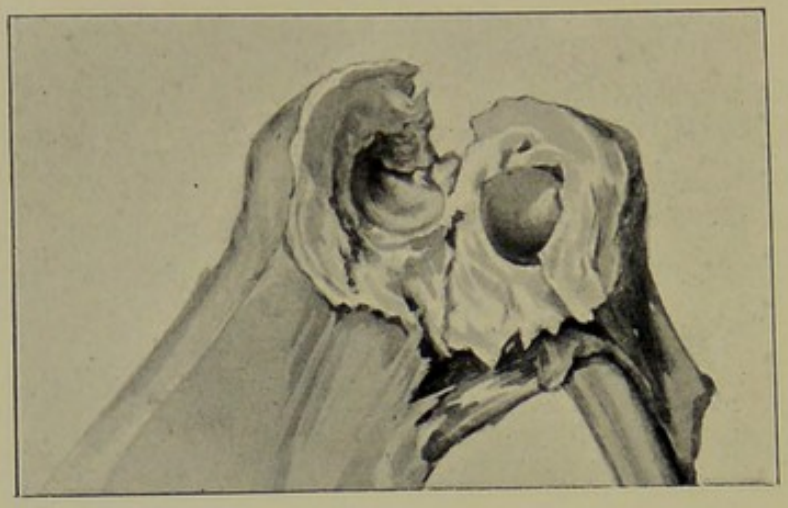


FIG. 35

The left shoulder-joint of a rabbit showing rheumatic arthritis (natural size). There is great thickening of periarticular tissues and joint capsule, the result of an arthritis due to the intravenous injection of the diplococcus. The cartilages were not affected. The exudation, considerable in amount, was clear. The arthritis was of three weeks duration, and other large joints were affected.

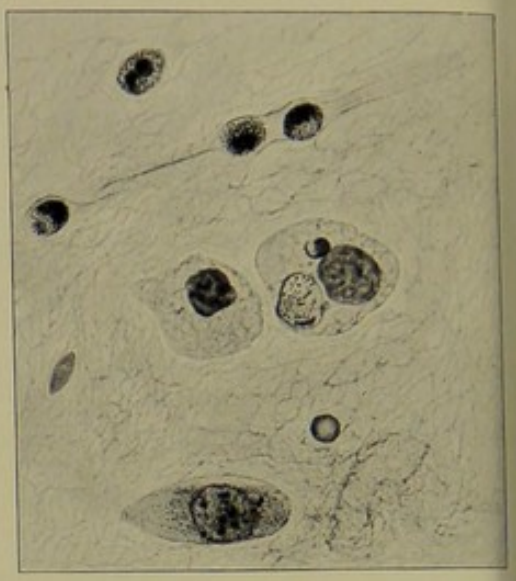


FIG. 36

Experimental rheumatic arthritis; film of the exudation showing a delicate fibrinous network with endothelial cells and a few leucocytes. Diplococci are seen in the endothelial cells.

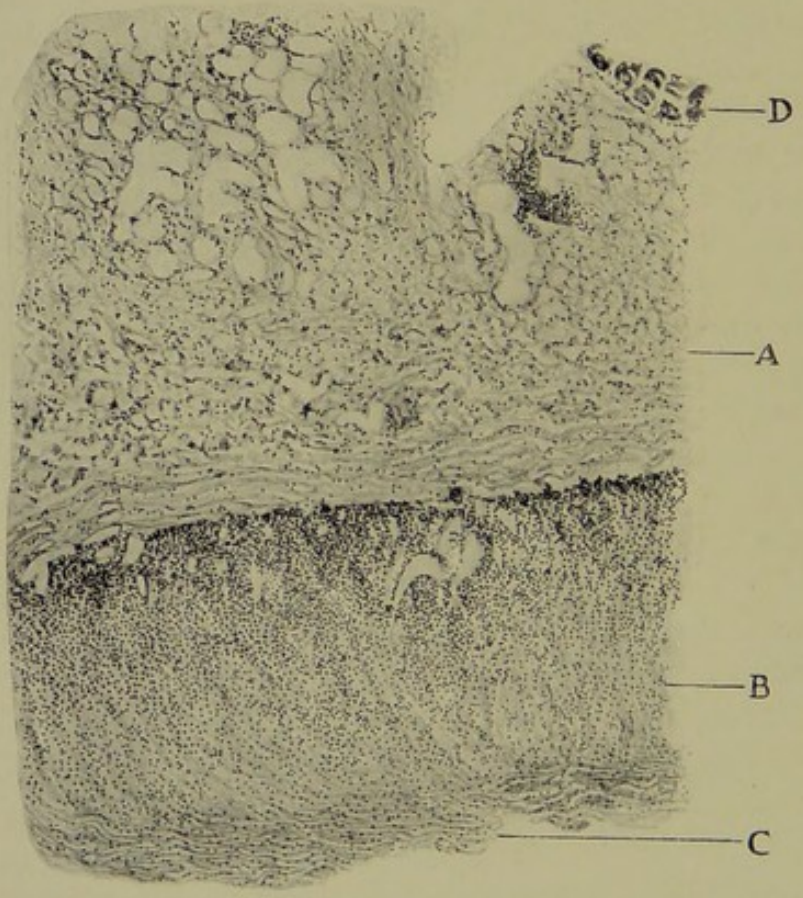


FIG. 37

Section through the capsule and synovial membrane of the kneejoint of a rabbit, showing experimental arthritis the result of intravenous inoculation with the diplococcus. (Under low magnification.)

A. Connective tissue of the capsule.
B. The synovial membrane infiltrated with leucocytes.
C. Fibrino-cellular exudation on the surface of the synovial membrane.
D. Muscular fibres.

Under high magnification numerous diplococci were seen in the synovial tissue and in the leucocytes.

rarely observed changes in the bones such as are seen in chronic rheumatoid arthritis.

We have brought for demonstration an affected and a healthy joint, together with the exudation from the diseased one, taken from a case which, we think, must be considered very striking. The culture was obtained from the mitral valve of a girl aged five years, who died in the Children's Hospital, Great Ormond Street, from a fatal first attack of rheumatic carditis. The demonstration of the organism from a fatal first attack of rheumatic fever is in itself an important point, and has a vital bearing upon the question of rheumatic fever considered as the result of a mixed infection, but on this occasion it must be sufficient to relate the experimental investigation which followed.

Upon April 16, 1901, after two days' incubation in a medium of ascitic bouillon, 1½ c.c. were injected intravenously into a rabbit. Three days afterwards there was a slight swelling of the left fore-limb; evident swelling of the left shoulder-joint quickly followed, remained for a fortnight, and then commenced to subside. The heart acted with great rapidity, but we failed to detect a murmur, though the animal was short of breath on exertion. The rabbit was killed three weeks after inoculation, and we removed in a sterilised pipette some of the fluid from the joint.

The distension of the joint capsule was well shown. The early mitral endocarditis and marked dilatation of the left ventricle, the mottled liver, small spleen, and pale kidney (the specimens of which were shown) are very characteristic of the disease in the rabbit.

A film of the exudation from the joint shows a delicate fibrinous network, a few red blood-corpuscles, some endothelial cells, and a few leucocytes. Of these leucocytes some show numerous coarse granules in their protoplasm, staining a red colour with eosin; others show no such granules. In some of the endothelial cells leucocytes can be seen in various stages of destruction; in others the organisms can be seen in the form of micrococci, though occasionally a diplococcal form is still visible.

In another case of arthritis of three days' duration, the synovial membrane looked to the naked eye almost natural; the fluid was blood-stained and contained a few flakes. The microscopic section of the synovial membrane was of interest,

because it showed in the delicate areolar tissue which binds the endothelial lining to the fibrous capsule a very extensive cellular exudation, which in places was distinctly fibrino-cellular. In this position the organisms occur, and it is here that they can be found in rheumatic synovitis. It is easy to understand, after a study of the section, the difficulty there is in obtaining a culture from the joint in a rheumatic arthritis of moderate severity, for the reaction is great, and leucocytes and endothelial cells rapidly destroy the organisms. *The acute and clear effusions both in rheumatic fever and in experimental arthritis are usually sterile.*

Another interesting feature in this section was the occurrence of an interstitial cellular exudation between the fibres of the muscles surrounding the joints. This may throw some light on the muscular pains which are so frequent in the rheumatic fever of childhood.

Under a third microscope there is a section demonstrating the fibrino-cellular type of exudation—that which we compare to the plastic type of pericarditis. Leucocytes which stain well and are not necrotic can be seen lying entangled in a delicate fibrinous reticulum.

The last specimen is a joint showing the gelatinous swelling of the fibrous structures which occurs in the acute stage of the arthritis ; this arthritis was produced by the intravenous inoculation of a culture obtained from another fatal first attack of rheumatic fever.

To summarise : Arthritis in rabbits is frequent but not invariable in its occurrence. It is a polyarthritis, affecting especially the larger joints. It tends to recovery, but varies in severity ; there may be acute swelling of the fibrous tissues of the joint, which become gelatinous in appearance, and if the condition is chronic there is much thickening of the fibrous tissues. The exudation varies in character from a clear or blood-stained fluid to a thick, opaque, fibrino-cellular exudation. The diplococcus can be demonstrated in these exudations, though in the very early stages they are absent or scanty, and in the late stages they are either destroyed or occur in the form of solitary micrococci. They are destroyed by leucocytes and endothelial cells, and they probably gain access to the joint through the minute blood-capillaries in the areolar layer of the joint capsule.

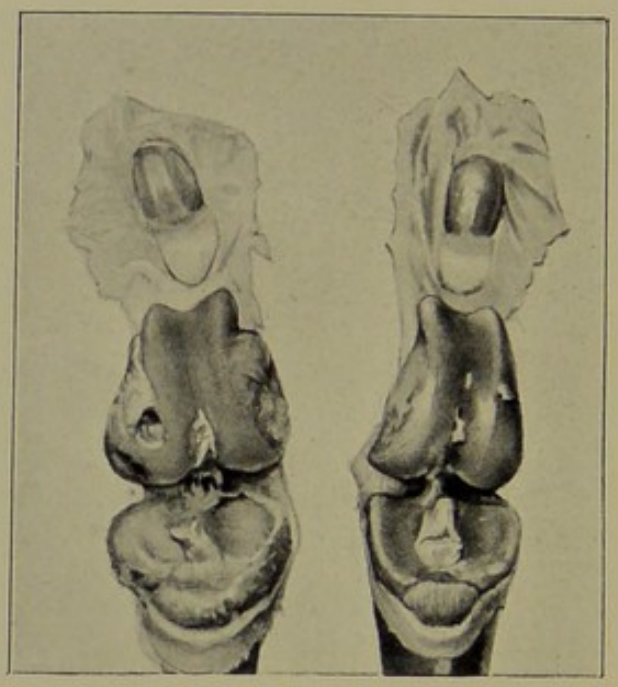


FIG. 38

Drawing of the knee-joints (natural size) of the rabbit referred to in the text. The left knee-joint (right in figure) is normal. The right knee-joint shows the following changes: (1) The articular surface of the femur is thickened and the cartilage has lost lustre. (2) The edge of the inner condyle is rounded and there is a prominence due to a new formation of imperfect bone and cartilage. (3) The edge of the outer condyle is rounded and lipped, and there is an area in which there is a destruction of bone and cartilage. (4) The articular surface of the tibia is flattened, the edges are much thickened and the cartilage has lost gloss (the cartilage when the specimen was fresh had a pitted appearance). (5) At the posterior aspect of the outer facet of the tibia there is a small area where the cartilage was destroyed (this can hardly be seen in the figure). (6) The crucial ligaments are swollen and have lost their lustre.

PAPER NO. XII

AN EXPERIMENTAL PRODUCTION OF THE OSTEO-ARTHRITIC TYPE OF RHEUMATOID ARTHRITIS

(Reprinted from the *Transactions of the Pathological Society of London*, 1902)

This paper has a special interest in being, so far as we are aware, the first record of an osteo-arthritis produced experimentally by the intravenous inoculation *of a micrococcus isolated from a case of human osteo-arthritis.*

Although this is but a short communication, the result is clearly one of fundamental importance, and opens up the field of study of chronic non-suppurative arthritis. This result has an added interest when it is compared with those which we produced later with the diplococcus rheumaticus. Vide Paper XX.

Upon July 16, 1901, a man aged 67, who had taken carbolic acid by misadventure, was admitted unconscious to St. Mary's Hospital, and died upon the 18th.

At the necropsy we found that several of his joints were crippled by a chronic destructive arthritis ; this was especially the case with the tarsal joints of the left foot, the left knee-joint, the terminal phalangeal joint of the right index finger. On movement of the knee there was grating. The joint contained two drachms of a clear, glassy, straw-coloured fluid, in which floated a few flakes of exudation. The structures of the articulation were much diseased ; the synovial membrane was much thickened, and in places hyperæmic ; the cartilage over the outer facet of the patella was completely destroyed, as also in great part those over the articular surfaces of the tibia and femur. When the cartilages had not been destroyed they had lost their gloss. The bones were eburnated at the points of pressure. The fibrous capsule was moderately

thickened, but the changes were essentially within the joint itself. Lastly, floating in the synovial fluid was a loose body, the size and thickness of a threepenny piece, probably formed by the organisation of inflammatory exudation.

The condition was clearly one of non-suppurative, chronic, destructive arthritis. The extensive erosion of the cartilages and the eburnation of the ends of the bones separated it from the group of chronic simple rheumatic arthritis. In the ordinary sense of the word, it was not a gouty joint, for there was no deposit of biurate of soda ; from the character of the fluid it could not be called a suppurative arthritis. It must therefore be classified among those chronic destructive joint lesions included under the name of rheumatoid arthritis, and among those in that group which we especially associate with later life. The cardiac valves were normal, and there was nothing discovered post mortem to show that the patient had suffered from previous attacks of rheumatic fever.

The Microscopic and Bacteriological Investigation

A few diplococci were found in a film made from the exudation in the knee-joint.

Some pieces of the synovial membrane were fixed in perchloride of mercury, and others incubated in the acid milk medium that we have used for the culture of the diplococcus of rheumatic fever.

The sections that were cut of the incubated and unincubated synovial membrane showed the presence of diplococci situated especially in the fringes.

The cultures showed a growth of diplococci and of the *Bacillus coli communis.*

The diplococcus was isolated on blood agar plates and transferred to blood agar tubes.

Experimental Results

I. Upon July 24, 1901, the cultures from two blood-agar tubes were injected intravenously into a rabbit. Two days afterwards there was arthritis of the left carpus, later arthritis of the left shoulder, and then of both knee-joints. There was no clinical evidence of morbus cordis.

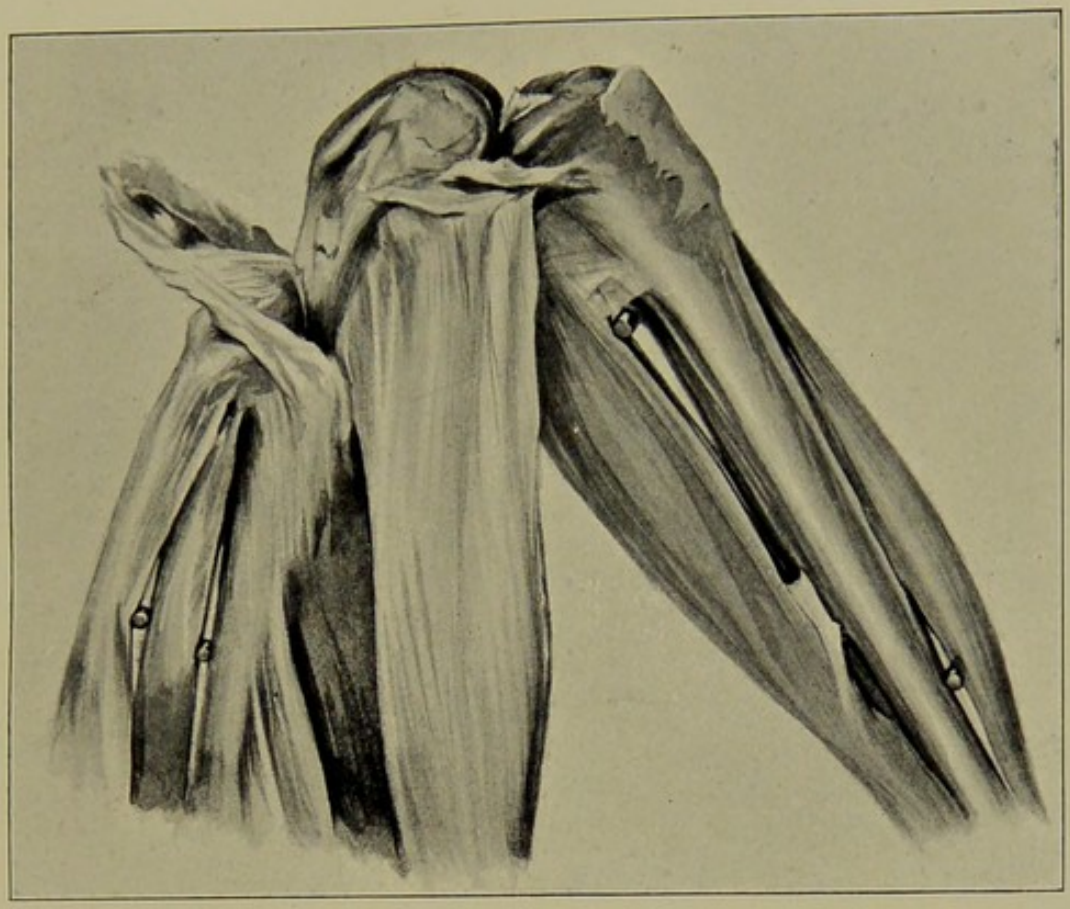


FIG. 39

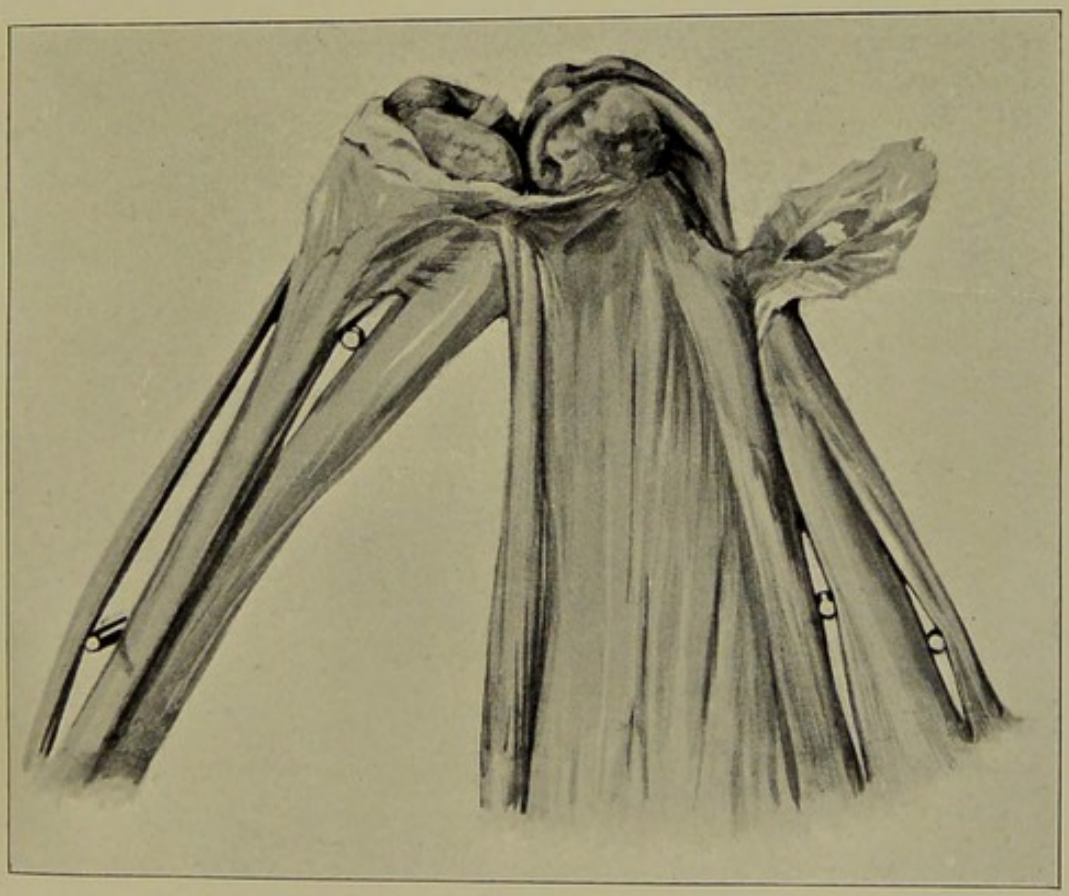


FIG. 40

A dissection of the hind limbs of the rabbit, the inner aspect of each limb is represented. Fig. 40 shows the atrophy of the muscles of the right limb. Fig. 39 shows the normal size of the corresponding muscles.

The animal was killed upon August 8, and a white fluid containing flakes of exudation was found in each of the affected joints. In the films diplococci were demonstrated, and the leucocytes stained well and were not necrotic.

There was no erosion of the cartilages, the heart was not affected, and there were no visceral lesions.

Thus from the first inoculation a severe multiple arthritis had resulted.

II. Upon July 30 another intravenous inoculation was made into a rabbit.

Throughout September nothing was noticed but some slight wasting of the right hind limb. The first week in October we found a slight excess of fluid in the right knee-joint.

The remarkable feature of this case was the definite atrophy of the muscles of the thigh and leg. At the end of September the limb was practically useless, and the atrophy very obvious. In the second week of October, ten weeks after inoculation, as there seemed a slight recovery of power in the limb, we killed the animal.

There were no visceral lesions, but the right knee, the only joint affected, contained a slight excess of a clear fluid, part of which was preserved in a sterilised pipette, and part of which was used for inoculation of a culture tube. The right knee-joint was enlarged, and the articular surfaces distinctly though slightly flattened. The edges of the articular surfaces were rounded, and, if compared with the corresponding joint, will be seen to be thickened, as the result of some lipping. A thickening on the inner condyle of the femur was especially noteworthy.

In two places on the outer condyle of the femur the bone was eroded and the cartilage destroyed.

There was both bone formation and bone destruction.

The cartilage on the tibia had lost the natural gloss, and with a lens was seen to be roughened and pitted.

There was also on the outer side of the epiphysial cartilage of the tibia at its posterior limit a small erosion with destruction of cartilage.

The atrophy of the muscles around the joint was very evident; the muscles on the anterior and posterior aspects of both leg and thigh were affected.

The joint capsule was not greatly thickened, but the ligaments, especially the crucial, were opaque and swollen.

The culture from the joint was sterile.

Thus in this case there resulted from an intravenous inoculation of a diplococcus, isolated from a case of chronic rheumatoid arthritis, a monarticular arthritis, with excess of clear fluid in the joint cavity, erosion of cartilage and bone, alteration in the shape of articular surfaces, and marked atrophy of the muscles in the neighbourhood. The injury to the joint was therefore of the nature of an osteo-arthritis rather than a synovitis and capsulitis such as we have observed in the experimental arthritis produced by the diplococcus of rheumatic fever.

The view that some cases of rheumatoid arthritis are of microbic origin has been long maintained, and as early as 1893 Max Schüller described the occurrence of bacilli which exhibited polar staining as present in the joint exudations, and various investigators have contributed to our knowledge of the bacteriology of rheumatoid arthritis.[1]

For example, in this country the researches of Bannatyne, Wohlmann, and Blaxall, published in 1896, are well known.[2] The organism described by them was also a bacillus which was cultivated by Dr. Blaxall.

Chauffard and Raymond, later, in 1896, also isolated a diplobacillus from the synovial fluid and scrapings of the lymphatic glands, but failed to obtain cultivations.[3]

In 1898, von Dungern and Schneider isolated a minute diplococcus from a case of rheumatoid arthritis which had apparently followed rheumatic fever.[4] This diplococcus injected directly into the knee-joint of a rabbit produced changes which they believed to be rheumatoid.

In this investigation of ours it is an interesting point that a monarthritis of this type should have followed an inoculation *into the general blood-stream.* Whatever the cause or causes of rheumatoid arthritis may be, this appears to be quite certain : that if it is the result of any infection the paths of access are far distant from the joints, and these structures are damaged because they are peculiarly susceptible, and not because there is direct invasion by micro-organisms as in traumatic arthritis, the result of a punctured wound.

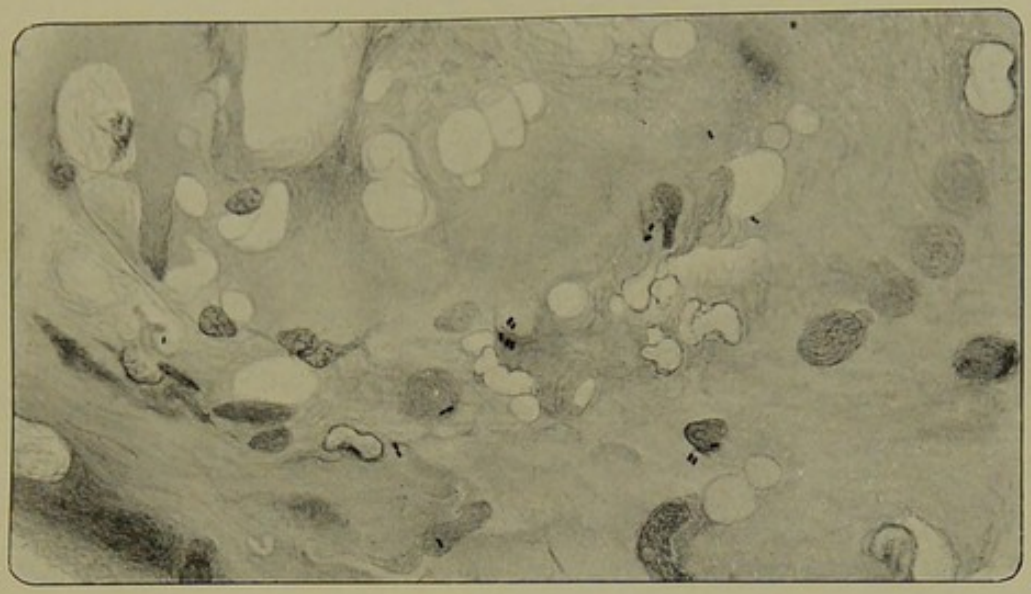


FIG. 41

Section through the synovial membrane of the knee-joint from a case of osteo-arthritis, showing diplococci. (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

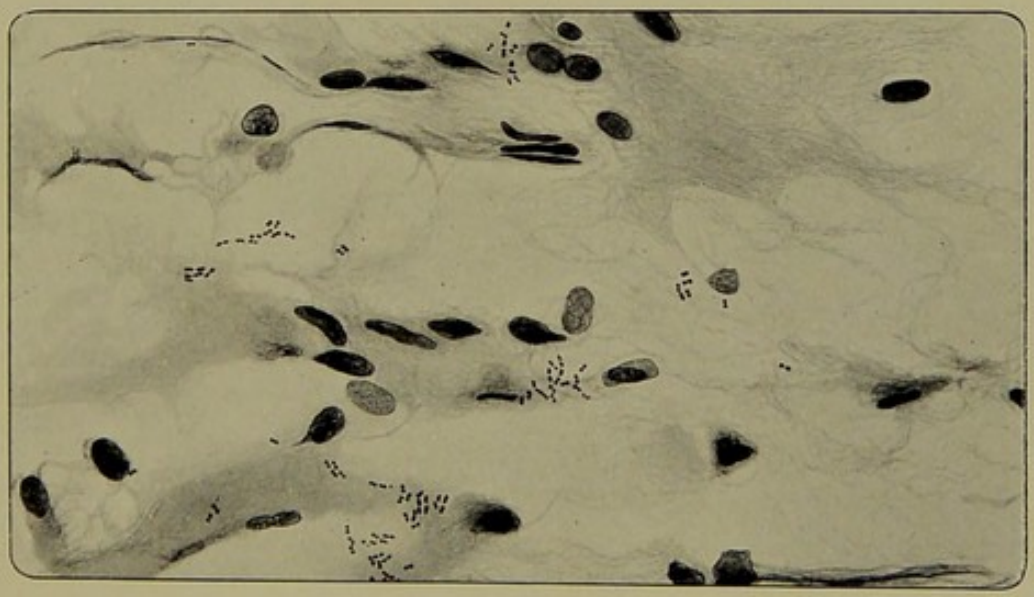


FIG. 42

Section through the synovial membrane of the knee-joint of the same patient as Fig. 41. The tissue had been incubated for twenty-four hours in the acid-milk and bouillon medium. Showing diplococci. (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

To Summarise the Conclusions.

1. A diplococcus was present in the synovial membrane of the knee-joint of a man aged 67, several of whose joints showed the chronic destructive changes recognised as occurring in one type of rheumatoid arthritis.

2. This diplococcus was isolated and cultivated in pure growth, both on blood agar and in a medium of milk and bouillon acidified with lactic acid.

3. Upon two occasions when injected into rabbits it produced a severe arthritis but no cardiac lesion.

4. The organism was isolated from the exudation occurring in the joints of the rabbit.

5. In the second instance a monarthritis resulted from the intravenous inoculation, which showed destruction and formation of bone and cartilage with some flattening and lipping of the articular ends and definite wasting of the muscles in the neighbourhood.

The capsular structures were little affected and the exudation was clear and sterile.

6. This arthritis differed in type from that which we have hitherto produced with the diplococcus of rheumatic fever.

We conclude, therefore, that—

7. This diplococcus was the cause of the arthritis in the case from which it was isolated, and of the condition produced by experiment in the rabbit.

REFERENCES

[1] Max Schüller, *Verhandlungen des fünfzehnten Cong. f. innere Med.* S. 127, 1892 ; *Berliner klinische Wochenschrift*, 1896, vol. xxx, p. 865.

[2] Bannatyne, Wohlmann, and Blaxall, *Lancet*, 1896, vol. i, p. 1120.

[3] Chauffard and Raymond, *Revue de Médecine*, 1896, vol. xvi, p. 345.

[4] Von Dungern and Schneider, *Münchener med. Woch.*, October 25, 1898.

PAPER NO. XIII

OBSERVATIONS UPON CERTAIN FORMS OF ARTHRITIS

(Reprinted from the *British Medical Journal*, November 1, 1902.)

In this communication the results of the previous researches into the pathology of arthritis are applied to clinical investigation with the object of directing attention to the importance of a detailed study of the exudations in arthritis. An attempt is made in it to put into their correct perspective the results of the preceding paper, with particular reference to those conditions generally termed "rheumatoid arthritis."

THE pathology of arthritis has of recent years attracted considerable attention, and surely, though perhaps it may be slowly, we are being led to a more thorough knowledge of the morbid changes, and in consequence to a broader view of the treatment of such cases. If, then, in this paper, we refer especially to our own investigations, we would not have it thought that we are unaware or forgetful of the work of others. We do so, because the time at our disposal is necessarily limited, and can be put to a better use by a reference to our own observations than by making quotations from the investigations of others of which we have ourselves no personal knowledge.

The types of arthritis to which especial attention will be directed are the rheumatic, the rheumatoid, and septic, although incidentally other types—for example, those which result from infection with the pneumococcus and the gonococcus—will need a passing mention.

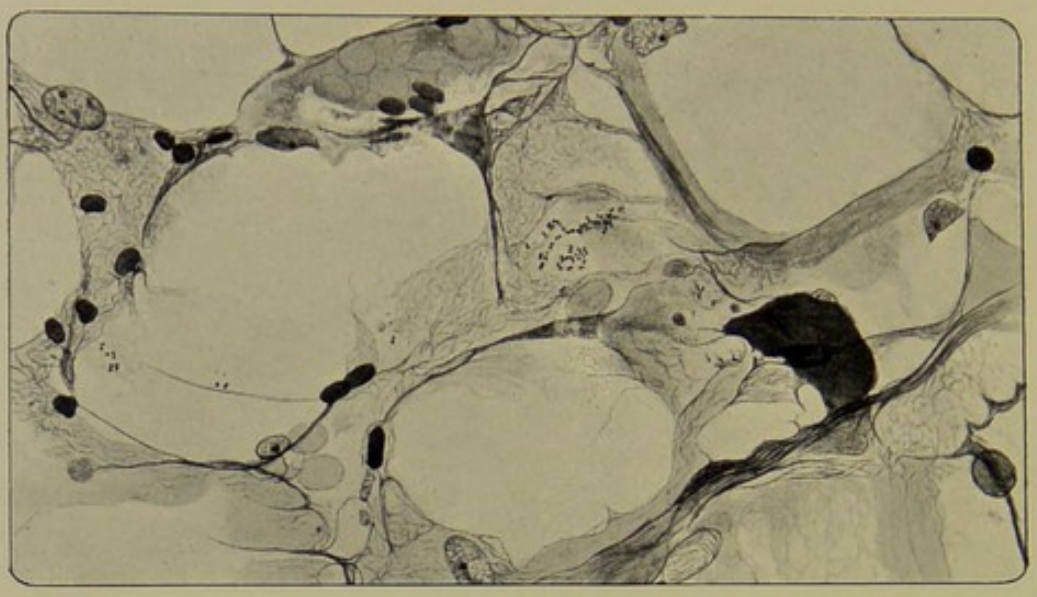


FIG. 43

A section through the synovial membrane from the knee-joint of a girl who died from rheumatic carditis, showing the diplococci in the areolar tissue. During life the knee had been slightly swollen and tender. The exudation was clear except for a few flakes; from it the diplococcus was isolated in pure culture.

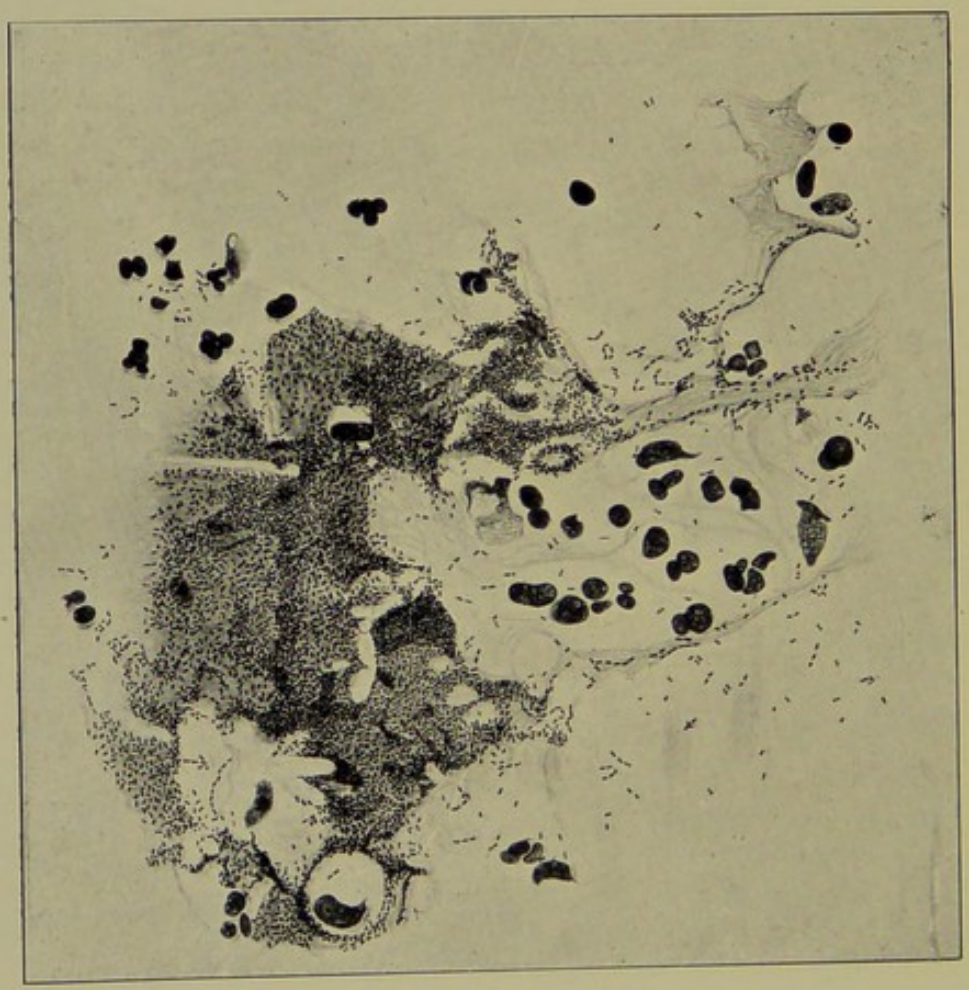


FIG. 44

Film of the exudation from the knee-joint of a boy suffering from rheumatic arthritis. A special feature of interest is the great number of diplococci present in the exudation. Complete recovery resulted.

Rheumatic Arthritis

In the *Lancet* of September 1900, we recorded in a paper upon the etiology of rheumatic fever the following experimental results :

A man, aged 28, came to St. Mary's Hospital in June 1900 suffering from a "sore throat." His illness had commenced with *malaise* and pains in the limbs and joints. Four years before he had passed through a severe attack of rheumatic fever, which had left both the mitral and aortic valves damaged and incompetent. The catarrh and injection of the throat were such as are met with frequently in rheumatic angina. The heart was excited and dilated, and, after his admission into the hospital, the man had another attack of rheumatic fever. By means of plate cultures we isolated from the tonsils some minute diplococci which resembled those we had already isolated from seven cases of rheumatic fever, and which had been obtained from various tissues—from the pericardial effusions, the cardiac valves, and the blood of the living patient. An intravenous injection into a rabbit from the blood agar cultures resulted in the death of the animal from mitral endocarditis, pericarditis, pleurisy, and pneumonia. The diplococcus was isolated from this animal, and from an injection into a second there developed a polyarthritis, from which after three weeks the rabbit completely recovered.

It is evident that a patient suffering from rheumatic fever harboured in his throat numerous minute diplococci which were capable of producing in an animal symptoms indistinguishable from those from which the patient himself was a sufferer.

It has always appeared to us that these results have a very important bearing on the study of rheumatic arthritis, and we were glad to find that a physician of the experience and position of Dr. Stephen Mackenzie, and moreover an authority on rheumatic fever, has also believed them to be valuable, and has alluded to them in his recent and most suggestive oration to the Medical Society of London. Fritz Meyer, at Berlin in 1901, has also confirmed in many points these results, on a more extensive scale and quite independently, and the early researches of Loeffler on the streptococcus articulorum must also be mentioned.

The ability to produce experimental arthritis has enabled us to study various phases of rheumatic arthritis, and to support our clinical facts by investigations of this nature. The morbid processes in this form of arthritis seem to us to run the following course.

The micro-organisms first gain access to the synovial membranes by means of the blood stream, and then make their way out of the blood capillaries which lie in the areolar tissue immediately under the endothelium which bounds the synovial cavity. This endothelium serves as a barrier to their escape into the cavity of the joint, and the cells which are phagocytic, can sometimes be seen to have proliferated in response to the infection. Further, into the areolar tissue in which the diplococci are located there migrate a large number of leucocytes, and they also assist in the destruction of the invader. On the other hand, the micro-organisms rapidly exert an injurious effect upon the tissues. The blood capillaries are distended, and may rupture, the connective tissues are swollen, and into the cavity of the joint there is exuded a clear or blood-stained fluid. Yet while the endothelium is intact the micro-organisms do not, at any rate in any number, escape into the fluid, and as our experience has repeatedly shown, these early exudations are often sterile.

We would emphasise that this escape of the micro-organisms into the joint cavity is a *vital* and not a passive process—one, therefore, which not only is difficult, but which may not even be successful. Indeed, the realisation of this truth is, we believe, of far-reaching importance in the study of rheumatic affections.

As a rule the morbid changes in rheumatic arthritis go no further ; the micro-organisms are destroyed, the exudation is absorbed, and the function of the joints is restored. Yet sometimes, as we know, the arthritis may be more severe, and then the periarticular tissues become swollen, the tendon sheaths in the neighbourhood are implicated, and the skin over the articulations is red and hot. Then, too, the fluid in the joints becomes turbid, and layers of fibrino-cellular exudation may line the cavities. In such cases the endothelium is damaged and the diplococcus can be isolated from the effusion in which it clings closely to the fibrinous

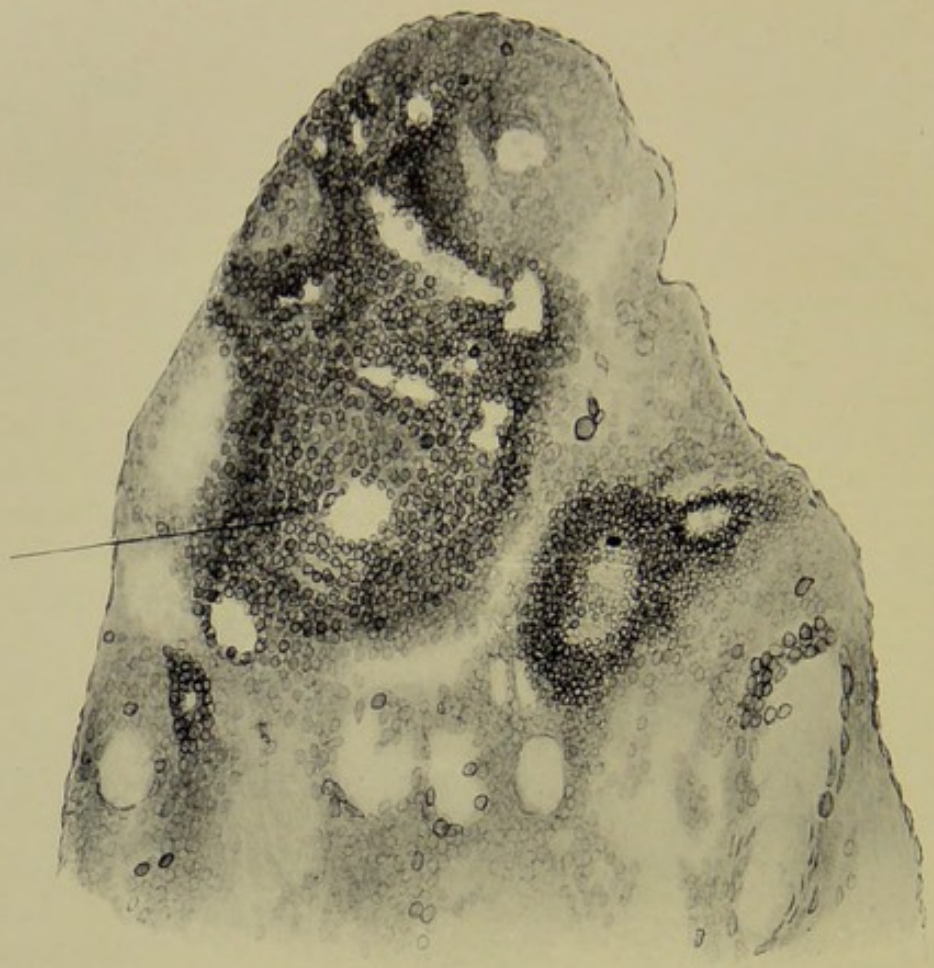


FIG. 45

Section through the synovial membrane of a rabbit with experimental rheumatism, showing early perivascular exudation. (High power.)

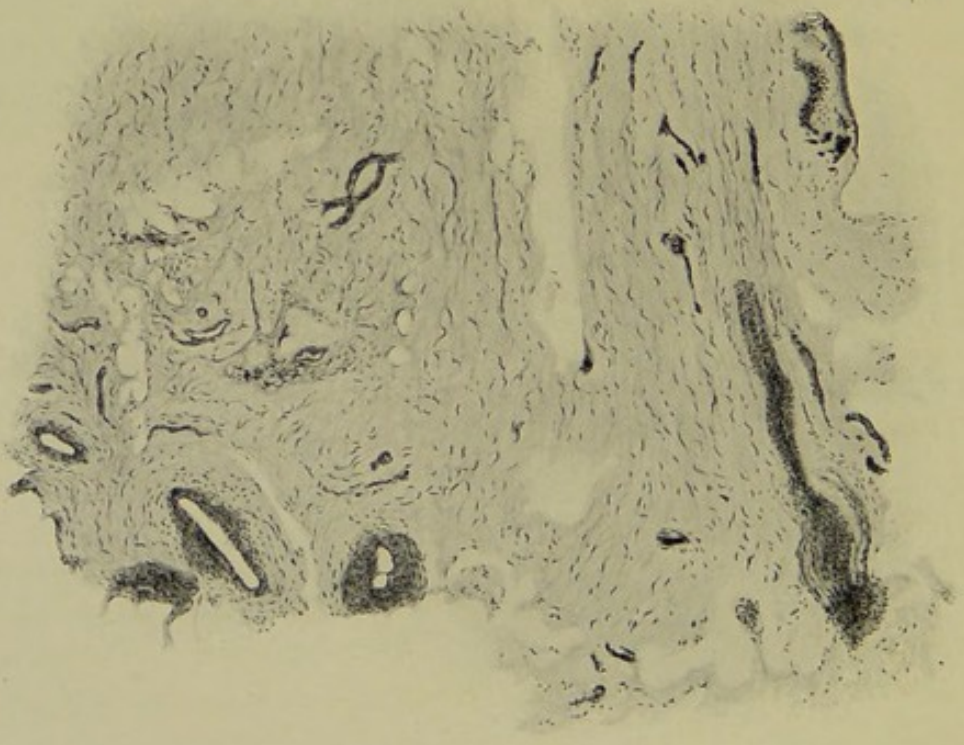


FIG. 46

Chronic rheumatic arthritis (human), showing perivascular fibrosis in the synovial membrane. (Low power.)

strands. For a long time the joint remains stiff, but as a rule the bones and cartilages are not damaged to any great extent, and experience has shown that assiduous after-treatment often results in a complete recovery.

There is another type of rheumatic arthritis not so acute as the one that has just been mentioned, but more stubborn and intractable, and in these cases another series of morbid changes is superadded. These changes are such as are met with in all chronic rheumatic lesions, and they can be well studied in the myocardium. Around the blood capillaries and arterioles there is at first a cellular exudation, and later a perivascular fibrosis. This newly formed fibrous tissue around these small blood vessels obeys the usual rule, and slowly contracts, diminishing thereby the blood-supply and nutrition of the synovial tissues. We have on several occasions commented upon this perivascular fibrosis, which it may be said is in no way peculiar to rheumatic fever, but we are indebted to Dr. Chalmers Watson for pointing out to us its importance in chronic rheumatic arthritis. This occurrence may in part explain the feeble circulation in such joints, the dropsical character of the effusion, and the slow and imperfect reaction to all methods of treatment. It must not be forgotten that in the effusions which are passive rather than active no micro-organisms may be present, and the cultures therefore be often negative.

These three types of arthritis are generally recognised by English authorities as rheumatic rather than rheumatoid in nature, though it must be admitted that these two conditions approach one another very closely, a point to which we shall allude again.

An Infantile Arthritis described by Dr. G. F. Still

The next group of cases is a very interesting, though somewhat rare form of arthritis in childhood, which has been admirably described by Dr. G. F. Still. This is of a chronic type, the changes are periarticular rather than intra-articular, the lymphatic glands are enlarged, as also the spleen. In fatal cases general adhesion of the pericardium has on more than one occasion been discovered after death, and this without endocarditis. Dr. Parkes Weber, who brought such a case before the Medical Society of London this year, was of

opinion that this was a form of infantile rheumatism. Many observers believe this group to be a form of rheumatoid arthritis, while others suspend their opinion. We had an opportunity of investigating Dr. Weber's case during life, but the result was negative. Such a negative result, however, means little or nothing, and there can be but slight room for doubt that this type of arthritis is of bacterial origin, and the likelihood is increased by the fact that from cases of rheumatoid arthritis with enlarged lymphatic glands. Chauffard and Raymond from scrapings of these glands isolated diplobacilli. We would add that the lymphatic glands are sometimes enlarged in the neighbourhood of the inflamed joints produced by experimental intravenous inoculation of rabbit with the diplococcus of rheumatic fever.

Rheumatoid Arthritis

The mental transition from these cases to those of rheumatoid arthritis is easy, but the difficulties that surround the study of the latter are very great. One of the difficulties which at once meets an investigator is uncertainty in the limitation of the disease. Is rheumatoid arthritis a special constitutional disease, in which the arthritis is a prominent feature, comparable, as it were, to the carditis of rheumatic fever, or is it a collection of morbid conditions with these features in common—a severe and intractable arthritis, accompanied with much muscular wasting ? So far as the arthritis is concerned, it would appear that several infections may lead to such results. For example, gonorrhœa, influenza, puerperal infections, and sometimes rheumatic fever. But apart from arthritis of this type, which can be traced to some definite infection, is there still left a special disease of bacterial or non-bacterial origin, which should be called rheumatoid arthritis ? In other words, much the same problem arises with rheumatoid arthritis as has arisen with rheumatic fever, the problem as to whether or not it is a specific disease.

Since Max Schüller first described micro-organisms in connexion with rheumatoid arthritis, many observers have added to the literature ; and in England Drs. Bannatyne, Wohlmann, and Blaxall have contributed most important papers to this subject. The difficulty which strikes all who have followed

these investigations has been the explanation of the negative results which have followed experimental inoculations. It is clearly not sufficient to inject directly into the joint any micro-organisms which may have been isolated, for the infection in man does not take place in this direct way. The interest of an investigation we brought before the Pathological Society of London early in this year lies in the fact that we produced the lesions of rheumatoid arthritis in rabbits by intravenous inoculation of a diplococcus. The investigations did not claim to demonstrate that the cause of rheumatoid arthritis was a diplococcus, for in the present state of our knowledge of this disease, and on the evidence of a single observation, such a claim would have been unjustifiable, but it demonstrated that these lesions could be produced by an organism injected into the blood stream, and not directly into the joint, the lesions including in addition to arthritic changes much wasting of the muscles of the limb.

Nervous Lesions in Rheumatoid Arthritis

Rheumatoid arthritis is remarkable, we know, for the severity of the nervous symptoms. They are so obtrusive as to have given rise to the widespread belief that the change in the joints is in reality a neurotrophic phenomenon. But at the present time, although it is beyond dispute that the nervous system is profoundly affected, there is considerable doubt about the relation that exists between such nervous lesions and the arthritis. Dr. Triboulet, in a paper upon chronic rheumatic arthritis, has alluded to this difficulty in a comment upon a necropsy he had made at the Salpêtrière on a woman, aged 19, who had died while suffering from a severe chronic arthritis accompanied by extreme muscular wasting. The spinal cord showed a system degeneration of the posterior columns in the dorsal region, of Goll's column in the cervical, and a degeneration of the posterior nerve roots in the lumbar region, the result of a local meningitis. Dr. Triboulet remarks that, had not the history of this case been carefully recorded, it would have been easy to have explained the arthritis as secondary to the meningo-medullary changes. The history, however, showed that both the arthritic and the neural changes were the common result of a puerperal

infection. This case seems to us to define the present position very clearly, and we may state it in the form of this interrogation: Are not the nervous and the arthritic phenomena of rheumatoid arthritis the common result of some poison which has a special affinity for these structures?

Rheumatoid Arthritis and Rheumatic Fever

The close relation of rheumatoid arthritis to rheumatic fever has certainly been long recognised by the medical profession.

Many years ago Sir Samuel Wilks compared the rheumatoid changes in rheumatic fever to malignant endocarditis in rheumatic patients. Dr. Herringham, among those who joined in the discussion last year at Cheltenham, especially emphasised the close association of these two diseases. Perhaps the most accepted view about such cases is that a secondary infection has been superposed on the primary rheumatic disease.

We have demonstrated that the rheumatic organism may produce both simple and malignant endocarditis, and it appears to us as highly probable that rather than that a secondary infection has been superposed in such cases, there is in reality an exalted local virulence of the original infection.

The usual clinical history that precedes malignant rheumatic endocarditis is one of repeated simple rheumatic endocarditis, and with these forms of rheumatoid arthritis there may be also a previous history of repeated attacks of simple arthritis.

It is a well-established fact that if a micro-organism is injected into a resistant animal, and yet, in spite of this resistance, succeeds in gaining the upper hand, the virulence of that micro-organism for this species of animals is thereby heightened. This is a fact of cardinal importance, and this property, inherent to the infective agent, cannot, we think, be overlooked. Yet it is sometimes said, even by those who support the bacterial origin of rheumatic fever, that the disease is entirely dependent upon the habit of body, that the infective agent is merely an excitant, and that there may be more than one such infective agent. To us this view appears incomplete. Most certainly the "soil" in rheumatic fever is of great importance, but not all-important, and we are not

at the present time, we think, in a position to state how important.

We believe it to be not improbable that some cases of rheumatoid arthritis associated with rheumatic fever are examples of this intensification of bacterial virulence. The repeated attacks of rheumatic arthritis which precede these attacks, and the imperfect recovery from them, point to an infection, quiescent for a while, but never conquered. The local virulence is raised by this survival against the resistance, and at length asserts itself. The type of the disease is altered to that which, when it attacks the heart, is called malignant, and the bones and cartilages, as well as the synovial structures, may all of them share in the destructive process. These progressive lesions, whether of the joints or of the cardiac valves, appear to us to be a more probable result of the exaltation of the virulence of the rheumatic infection than the development of a pyæmia.

So far as one dare express an opinion on that difficult question of the relation of rheumatic fever to pyæmia, it seems to us that, though analogous processes, they are essentially different in nature.

Pneumococcus Arthritis

Arthritis from an infection with the pneumococcus will not detain us long. To Dr. Cave, we believe, is due the credit of calling attention to this condition in England, and Dr. Nathan Raw and Dr. G. A. Murray have also advanced our knowledge upon this subject. We mention it here to give further support to their statements. On two occasions we have isolated this organism from cases of suppurative arthritis complicating pneumonia, and at the time we published our first results upon rheumatic fever we were alive to the occurrence of this form of arthritis, and did not fall into the error of mistaking the pneumococcus for the special organism which we then described.

Suppurative Arthritis

The study of suppurative arthritis brings us face to face with another difficulty which is essentially one of words. The two terms "septic" and "pus," though of great practical

convenience, are fast losing their value in scientific descriptions of arthritis. They are suffering much the same fate as the two other well-known clinical expressions—"hectic" and "typhoid state." Just as these were, so are these now, often employed to represent specific conditions when in reality they only represent certain clinical phases. The pneumococcus, for example, may produce pus, as also may the streptococci and staphylococci; and when those infections cause severe constitutional symptoms, the condition is often called in each case septic. Rheumatic fever, too, may perhaps, produce a pus, yet it can hardly be that the poisons which produce these suppurations are in each case the same. But it is essential that some substitute should be employed for these words otherwise we are left in a predicament. A useful, though incomplete, phraseology will have been removed and nothing put in its place.

It seems advisable at the present time to use as a substitute a description of the exudations in the joints which is detailed and yet which avoids these two terms, and in illustration of our meaning we give the following examples:

A lad, aged 14, was admitted, under the care of Mr. Herbert Page, at St. Mary's Hospital, in March of this year (1902), suffering from an arthritis of the left-knee-joint. The origin of the condition was obscure. The left knee-joint was tense with fluid, the temperature was raised, and at times the boy was slightly delirious. Ordinary methods of treatment had been ineffectual, and Mr. Page, from an experience of similar cases, decided to draw off the fluid and wash out the joint with a 1 per cent. solution of carbolic acid. This was done on two occasions, and after the second irrigation, as a result of our investigation of the fluid, full doses of sodium salicylate were given in addition. Complete recovery resulted.

Our investigation of the exudation gave the following results:

1. The appearance of the fluid was greenish and slightly opaque.

2. A film showed: (*a*) Numerous minute diplococci, some in chains, others in masses; (*b*) leucocytes and endothelial cells, which were not necrotic; (*c*) fibrin.

3. Culture on blood agar gave a pure and abundant growth of a diplococcus in minute discrete colonies.

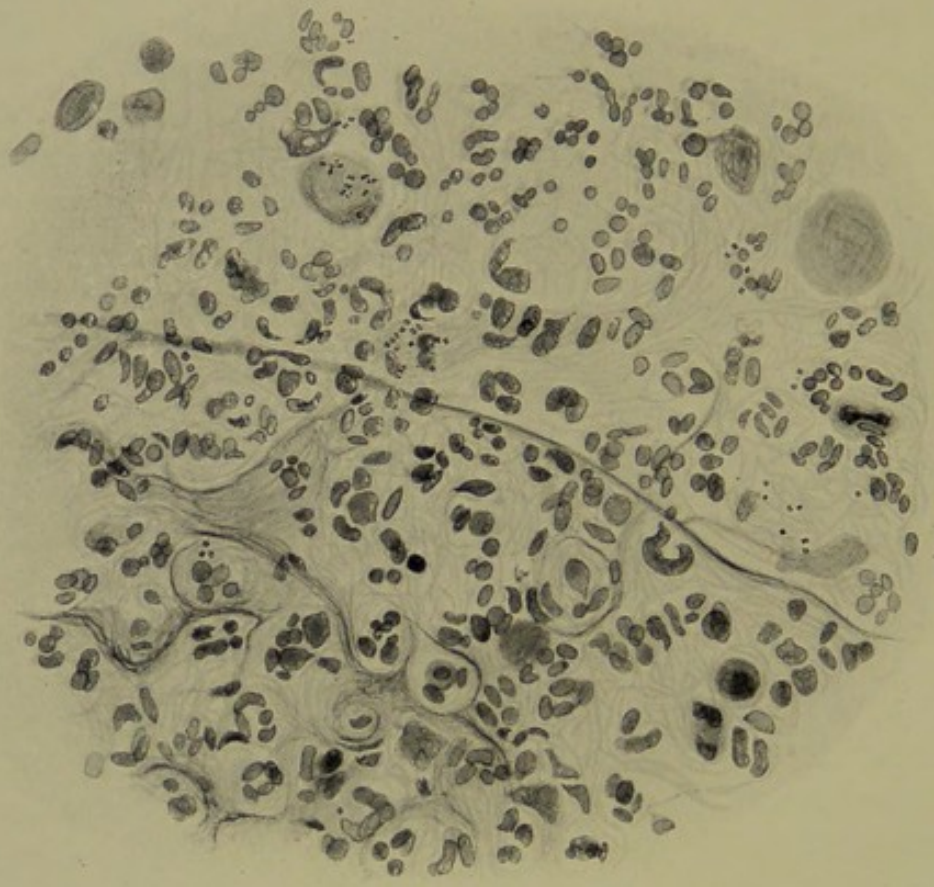


FIG. 47

Gonococcal arthritis (human). Film of exudation, showing gonococci, mainly intracellular. (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

4. Intravenous inoculation into rabbits produced multiple arthritis of all grades of severity, from those from which recovery was complete to those indistinguishable from severe types of rheumatoid arthritis.

It is clear then that the arthritis in this case was due to a diplococcus which had escaped the barrier of the synovial endothelium, had eluded also the leucocytes in the exudation, and was living free in the fluid in a virulent condition. The treatment adopted by Mr. Page was not only entirely supported by this investigation, but the character of the micro-organisms pointed to the infection as of the rheumatic type. When, then, the joint had been cleansed by the antiseptic irrigation, full doses of sodium salicylate possibly completed the cure. This case was brought by Mr. Page and ourselves before the Clinical Society of London earlier in the year.

Case II. An infant, aged 5 weeks, was brought to the Hospital for Sick Children in Great Ormond Street, in March of this year (1902), with the following history: In the second week after birth the left ankle-joint became swollen and tender, then other joints became involved, and when brought to us all the large joints were affected and full of fluid. The bursa under the right deltoid was also tense with fluid. The natural explanation appeared to be either a septic infection from the umbilical cord or a blenorrhagic arthritis, but the nurse, a sensible woman, declared the cord had separated in a healthy manner. The actual cause of the arthritis must, then, be left to surmise. The condition of the child was one of extreme gravity, the more so as experience has shown how often in these infants we have to deal with a multiple purulent arthritis. We took advantage of the distended bursa under the deltoid, and with precautions drew off the fluid into a sterilised pipette; even this slight operation was followed by alarming collapse, so feeble was the infant's strength.

The examination resulted as follows:

1. The fluid was slightly opaque.

2. The film showed numerous leucocytes which were not necrotic, and in some of them were a few micrococci; no micro-organisms were free in the fluid.

3. Cultures were negatives.

We advised delay before opening any of the joints, and in the meantime the infant was carefully fed and stimulated.

Complete recovery resulted without any operation, and when the child was seen a month after leaving the hospital the recovery was complete. We believe this detailed investigation of the fluid was a means of saving a life.

Case III. A young woman was bedridden with multiple arthritis of recent origin. She was unmarried, and no history of the cause could be obtained. All the joints recovered except the left ankle-joint, which remained obstinate to treatment and extremely painful. The arthritis was so severe and the pain so great as to demand exploration. The surgeon, from the appearance of the joint at the time of operation, was inclined to think the condition was tuberculous.

The investigation resulted as follows :

1. The fluid was blood-stained and yellow.

2. The films showed numerous gonococci, many within the leucocytes, but some also free in the fluid. There were numerous leucocytes, some of them disintegrating.

3. On culture a pure and abundant growth of the gonococcus on blood agar was obtained. Experimental investigation proved negative, which, we recognise as the usual rule in gonococcus infection.

In this case a doubtful diagnosis was made clear.

Case IV. A child, aged 18 months, was admitted to St. Mary's Hospital with arthritis of both knees. The skin over the joint was tense and shining, and the constitutional symptoms severe.

The result of the investigation was as follows :

1. The fluid was thick, yellow, and creamy.

2. The films showed numerous streptococci free in the fluid. There was no fibrin, and the leucocytes were necrotic.

3. A pure growth of the streptococcus pyogenes was obtained on blood agar.

4. Intravenous inoculation into a rabbit resulted in death within twenty-four hours from septicæmia.

The inference from the investigation was that this was a case of severe streptococcus pyæmia, and the child died within two days.

We need not multiply instances to show that nothing is lost by the omission of the terms " pus " and " septic " from these descriptions, while, on the other hand, the danger of a stereotyped use of these words is avoided.

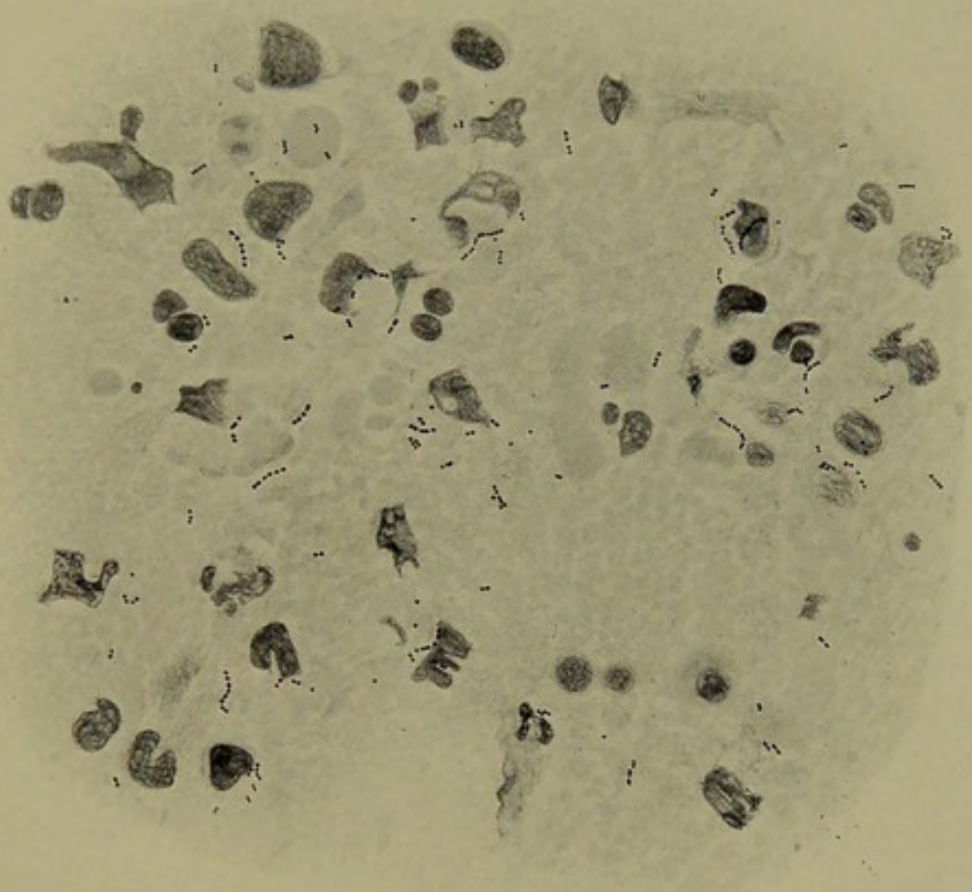


FIG. 48

Arthritis (human), due to the *Streptococcus pyogenes*. Film of the exudation showing the micro-organisms and cell necrosis. (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

In conclusion, it is clear that the treatment of arthritis is being gradually influenced by the realisation of the infective element in the causation. We need only mention in support of this that Menzer, at Berlin, in June, brought forward a specific serum for articular rheumatism. Such remedies will be received with great caution, but we must be prepared to hear more of them, and there is hope that eventually some success may be obtained in this direction. Meanwhile prophylactic medicine would appear to have a wide field before it, and more investigations on the lines of Dr. Newsholme's valuable Milroy lectures can hardly fail to be of interest.

In the arthritic subject the importance of the arrest of chronic discharges or ulcerations, the careful management of the throat, and the cleansing of the mouth are emphasised once more by these investigations.

Again, the realisation of the two elements, that of the infection and that of the resistance, impresses upon us the important fact that no one method of treatment can be suitable throughout the course of these illnesses.

Lastly, surgical interference, which has been so strenuously advocated from time to time, is undoubtedly put on a surer basis, though it is obvious that the suitable cases will always require careful selection.

PART II

SUB-GROUP C

THIS GROUP OF FOUR PAPERS WIDENS THE FIELD OF INVESTIGATION IN RHEUMATISM IN VARIOUS DIRECTIONS, AND OPENS UP NEW PROBLEMS, SOME OF WHICH ARE AGAIN CONSIDERED IN LATER COMMUNICATIONS

THE FOLLOWING ARE INCLUDED :

XIV. SOME FURTHER INVESTIGATIONS UPON RHEUMATIC FEVER

XV. A CONTRIBUTION TO THE STUDY OF MALIGNANT ENDOCARDITIS

XVI. A CONTRIBUTION TO THE STUDY OF RHEUMATIC IRITIS

XVII. THE RELATION OF THE STAPHYLOCOCCUS PYOGENES TO RHEUMATIC FEVER. By Dr. F. J. Poynton and Dr. W. V. Shaw

PAPER NO. XIV

SOME FURTHER INVESTIGATIONS UPON RHEUMATIC FEVER

(Reprinted from the *Lancet*, May 1901.)

This paper, published in 1901, *has been taken slightly out of chronological order because, with the other three in the first group, it helped to break new ground in connection with acute rheumatism.*

For the first time the true meaning of the rheumatic nodule was explained, and the result is the more interesting when this part of the paper is read together with Paper No. VI. The value of the method now well recognised as "reinforcing" is illustrated. The problem of the pathology of chorea is discussed in some detail, and the outcome of some further inquiries into the question considered and an explanation of the rheumatic form put forward. The occurrence of the diplococcus in the polymorphonuclear leucocytes is recorded. The incubation period of the disease and the probability of the occurrence of fever as a primary phenomenon are discussed. The great importance of the production of morbus cordis is illustrated by experimental observations.

Fritz Meyer's extensive researches upon rheumatic angina faucium had now been published, and in the main supported our contentions. We would, however, point out, as Fritz Meyer himself expressly stated, that he was unsuccessful in isolating the diplococcus he described, from other rheumatic lesions.

It is a curious fact that this weak point in Fritz Meyer's chain of evidence has been from time to time held to be present also in our investigations. We can hardly believe that those who have advanced his criticism can have seriously followed our papers.

SINCE our first contribution to this subject, we have continued our investigations and have now isolated the diplococcus from 16 cases of rheumatic fever. The particular point upon which we are still intent is to establish this diplococcus as a cause of rheumatic fever. If this can be firmly established then the many difficulties that must subsequently be faced can be dealt with from a firm basis. In no disease perhaps

more than in rheumatic fever is it necessary to make this ground sure, for it is in the centre as it were of a group of diseases, which not only may resemble rheumatic fever closely in their clinical features, but which are also the result of infections in all probability closely allied to that of rheumatic fever. The differential study of the streptococcal, staphylococcal, gonococcal, scarlatinal, rheumatic, and probably rheumatoid infections is one of great difficulty The morphological characters of the various organisms can only offer a partial assistance and chemical pathology has not yet advanced sufficiently to render much service, though the numerous researches both on the continent and in this country into the nature of the toxic processes due to microbic infections are indications of the importance of this subject. It is for these reasons that we have entered into such detail in our efforts to prove that this diplococcus is a cause of rheumatic fever, and it is upon this detail that we especially rely.

I. The Isolation of the Diplococcus from the Nodule

The first series of additional facts that we are able to bring forward in this paper is concerned with the rheumatic nodule. We have succeeded in demonstrating the organisms in two more nodules and have in addition grown them in the nodular tissue outside the body in pure culture. We have produced in a rabbit, as the result of an intravenous inoculation from this culture undertaken for us by Mr. H. G. Plimmer, pathologist to St. Mary's Hospital, a condition we believe to be that of acute rheumatism—namely, polyarthritis, pericarditis, and multiple valvular disease, all non-suppurative. Finally, we have isolated them in pure culture from the joints of the animal after death and thus completed the chain of proof. And since these formations are looked upon by general consent as highly characteristic of rheumatic fever, the isolation of this diplococcus from one of them will appeal to many as a strong link in the proof of the causal relation of this organism. A short outline of the investigation will give a clearer idea of the nature of this evidence. We are indebted to Dr. W. B. Cheadle for permission to make use of the clinical

notes of the case, and to Mr. H. G. Plimmer for the details of the necropsy.

A child, aged nine years, was admitted to St. Mary's Hospital on November 3, 1900, suffering from acute rheumatism. When four years old she had suffered from chorea and since then from three attacks of acute rheumatism. The present illness had commenced four weeks before admission with arthritis, and for three weeks there had been shortness of breath. The patient was pale and thin, the pulse-rate was 100, the temperature was 102.4°F., and the respirations were 40. There was dyspnœa and there was also advanced heart disease. Both the mitral and aortic valves were affected and the heart was dilated, but there was no sign of pericarditis. The knees and right elbow-joint were painful, but there was no effusion. Over both elbows and over the knuckles there were numerous small nodules. The urine contained a trace of albumin. At first the child seemed to improve, though it was noted that the nodules were increasing in size. On November 7, four days after admission, a condition of acute œdema of the lungs developed and proved rapidly fatal.

The necropsy showed recent transparent, bead-like vegetations upon the mitral, tricuspid, and aortic valves, and the mitral and aortic valves were also thickened from the results of previous inflammation. There was no pericarditis, but there were 25 cubic centimetres of a straw-coloured fluid in the pericardium. The lungs were œdematous and in some places there were hæmorrhages into the alveoli and in others collapse. The liver was "nutmegged," the spleen was small and firm, and both kidneys showed cloudy swelling of the parenchyma of the convoluted tubules. Two hours after death we removed three nodules from the right elbow with strict aseptic precautions. One of these we at once placed in the medium of milk and bouillon rendered slightly acid with lactic acid. The second we cut with a sterile knife, then scraped, and with the scraping inoculated a second tube. The third we "fixed" at once in perchloride of mercury. Both tubes were incubated anaerobically. The tube inoculated with the exudation remained sterile. The tube containing the entire nodule showed no growth upon the first day, but upon the third day a pure culture of the diplococci. The organisms were transferred to blood agar tubes and grew in the usual

small, white, discrete colonies. The contents of five of these tubes were injected intravenously into a rabbit on November 11. The result of the intravenous inoculation was as follows : The next day the heart was very rapid and there was a definite systolic mitral murmur, and upon the second day the hind limbs were stiff. The murmur then disappeared, but a week after inoculation the left fore and hind limbs were almost powerless, and in the next few days this weakness and stiffness spread to all four limbs. A fortnight after inoculation a systolic murmur had reappeared and there was definite pericarditis, but the stiffness had disappeared and the joints were none of them swollen. We were anxious to obtain a definite arthritis with effusion, because we have found that these effusions afford the easiest and most reliable local lesions from which to cultivate the organism. Accordingly, on November 26—that is, the day after we had noticed that the stiffness had disappeared—the animal was again inoculated with the organism which had been kept growing in the acid milk medium. Two days afterwards stiffness of the limbs appeared, then the right shoulder swelled, and five days afterwards both knee-joints. The animal was killed next day, and the post-mortem examination showed mitral and tricuspid valvular disease, pericarditis of some standing, and an opaque fluid in the right knee-joint. There was no suppuration in the viscera. Cultivations were taken from the joint and a pure growth of the diplococcus obtained. The nodule which had been incubated was by this time in a pulpy condition from the effects of the liquid medium in which it had been lying. This we fixed and hardened in alcohol and finally embedded and cut in paraffin. The nodule that we fixed in perchloride of mercury was also hardened and cut, and in the outer zone we found some groups of the diplococci. It will be seen from this account that every circumstance was favourable for the success of this investigation and the proof a very conclusive one. In our previous papers we also recorded that intravenous inoculations of the diplococcus had produced in one instance a nodule over a vertebral spinous process and nodular formations around the joints which microscopically resembled the structure of an early nodule in man. Also that subcutaneous injection of a virulent culture had produced a large swelling which, slightly

FIG. 49

Section through the outer zone of a recent rheumatic nodule, showing groups of the diplococci lying in the interstices of the swollen connective tissue. Removed two hours after death.

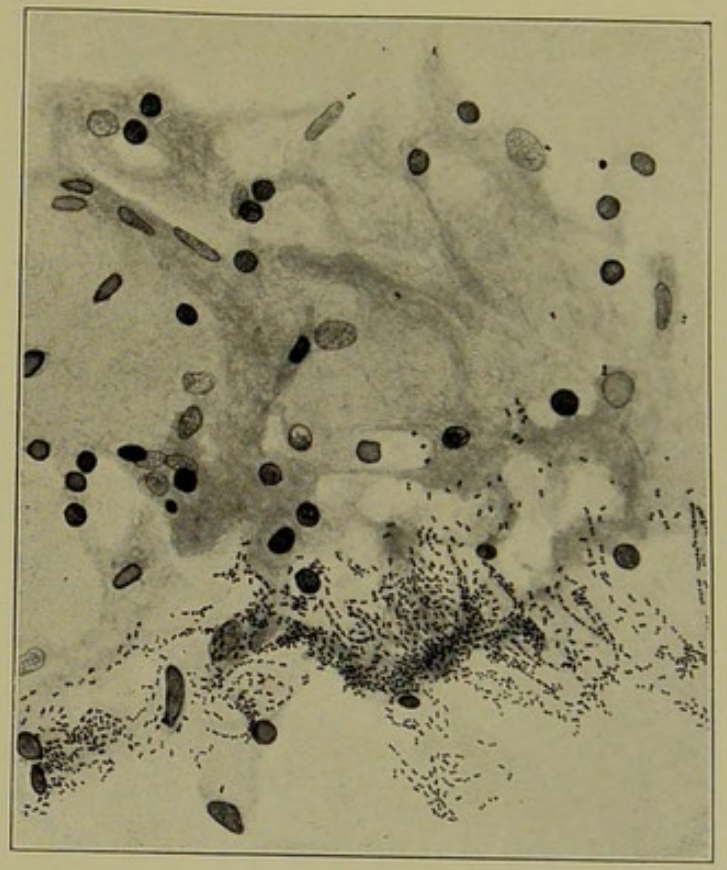


FIG. 50

Section through a rheumatic nodule removed two hours after death and incubated anaerobically in the acid-milk and bouillon medium. Numerous diplococci are present. (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

tender at first, had gradually disappeared without any evidence of suppuration.

This method of incubating the nodule may possibly be of some service to others who are interested in this subject. We believe that in the local lesions of rheumatic fever the struggle between the organisms and the tissues is so evenly balanced that in many instances at the time of death the diplococci are mostly destroyed. If, then, with due precaution, a lesion in the so-called "active" stage be removed and incubated in a suitable medium the organisms should grow, for there is now no resistance to prevent their growth. It is very possible that they do not regain their full vitality, but they can be easily demonstrated and may, as we have shown, produce experimental results. Recently we have adopted this method for the cardiac valves, and instead of curetting them have snipped off the granulations, incubated them in the acid medium, and in this way obtained a pure growth of diplococci.

Summary. To sum up, (1) we have demonstrated the diplococcus in three rheumatic nodules taken from two cases of rheumatic fever; (2) we have isolated the diplococcus from the nodule in one instance in pure culture; (3) intravenous inoculation of this culture has produced valvular disease, pericarditis, and polyarthritis in a rabbit; (4) we have isolated the diplococcus from the joint exudate of this rabbit; and (5) the nodule is looked upon as a highly characteristic manifestation of rheumatic fever. Therefore we conclude that this investigation lends strong support to the contention that this diplococcus is a cause of rheumatic fever.

II. Observations upon the Pathology of Rheumatic Chorea

In our paper upon the "Pathogenesis of Rheumatic Fever," read before the Pathological Society of London, in October 1900, we recorded a condition which we believed to be chorea produced by the intravenous inoculation of the diplococci into a rabbit. This rabbit was extremely nervous, and in addition manifested sudden irregular movements of the limbs and face. These movements were definite, but not violent, and there was about them that peculiar, sudden, involuntary

character, which is so characteristic of slight rheumatic chorea. At the time of the reading of this paper we had not examined the brain further than to be able to state that there was no visible meningitis. Since then we have investigated much of it, and have found diplococci in the pia mater and in the the endothelial cells of the blood capillaries, dipping into the motor cortex from the surface. The pia mater in places showed some slight swelling of its connective tissue and cell exudation. The organisms were also present in the walls of some of the blood-vessels of the pia mater. The rabbit which suffered from chorea, and also endocarditis and polyarthritis, was the only one in a series of inoculations from animal to animal that showed these movements. The others showed numerous manifestations of rheumatic fever, but not any movements of this nature. The fatal case of rheumatism, from which the culture was obtained, was recorded in Paper VIII, and the growth was obtained in the pericardial fluid itself after incubation. On another occasion we isolated the diplococci from the cerebro-spinal fluid of a rabbit suffering from endocarditis and pericarditis, but the animal had shown no signs of chorea. Again, we noted in a third rabbit weakness of the hind limbs, which we suggested might be paralytic chorea. In a case of fatal human chorea we discovered micrococci in the mitral valve and in the motor cortex, but the organisms were never isolated, and this observation at the best is not more than suggestive. Finally, on three occasions, we have isolated the organisms from the blood in acute rheumatic pericarditis. This is a proof in acute rheumatism with pericarditis that they may circulate in the blood stream, and therefore presumably in the cerebral vessels and thus may possibly escape to the cerebral tissues.

The conclusion to which these observations appear to lead is this—that the *commencement* of rheumatic chorea is associated with the presence of the diplococci in the brain and perhaps pia mater, as well as with the presence of toxins produced by these organisms. If this be so, then we should be prepared to find that, with due allowance for the special anatomical characteristics of the brain, the morbid changes produced would be analogous to those presented by other local manifestations of rheumatic fever. We can speak with confidence of the nature of these changes in the cardiac valves,

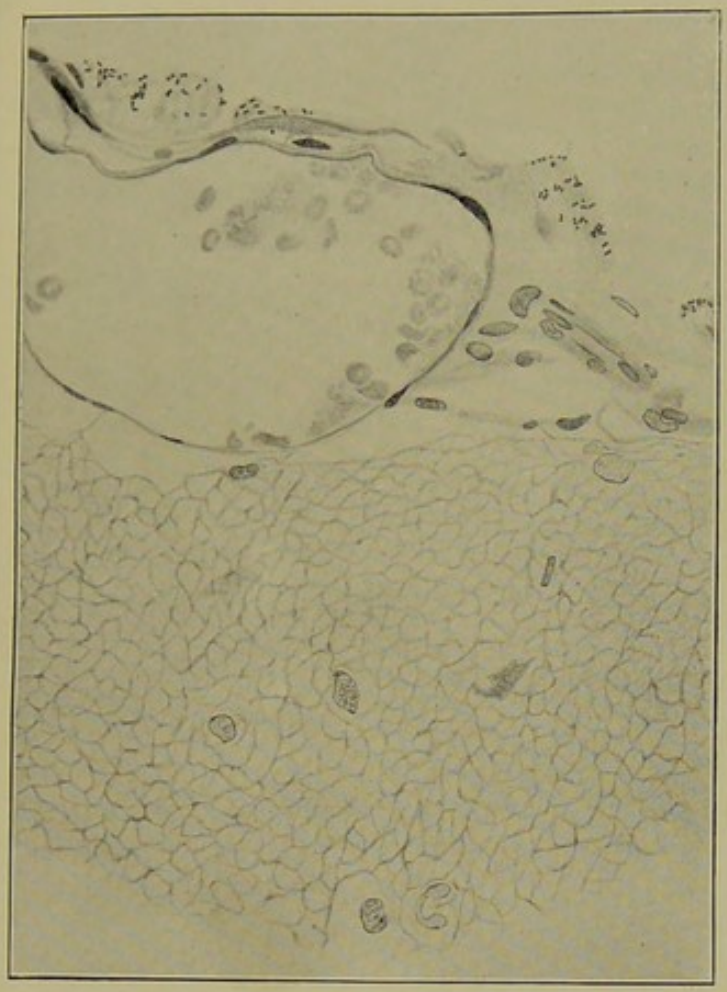


FIG. 51

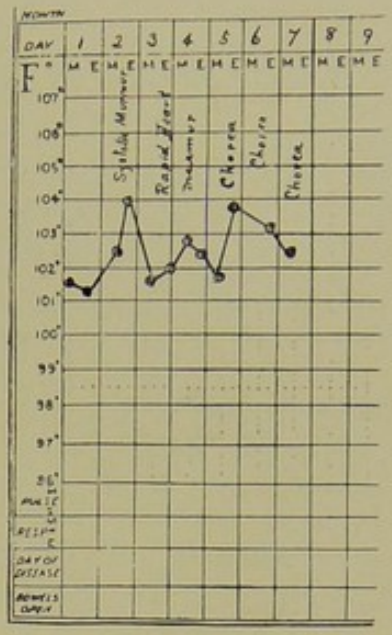


FIG. 52

Temperature chart of a rabbit which developed choreiform movements during an attack of experimental rheumatism.

FIG. 51. A section through the pia mater and adjacent brain tissue of a rabbit that suffered from polyarthritis, endocarditis, and choreiform movements, the result of intravenous inoculation with the diplococcus. Numerous diplococci are seen in the pia mater close to a large capillary blood-vessel; the pia mater is slightly swollen.

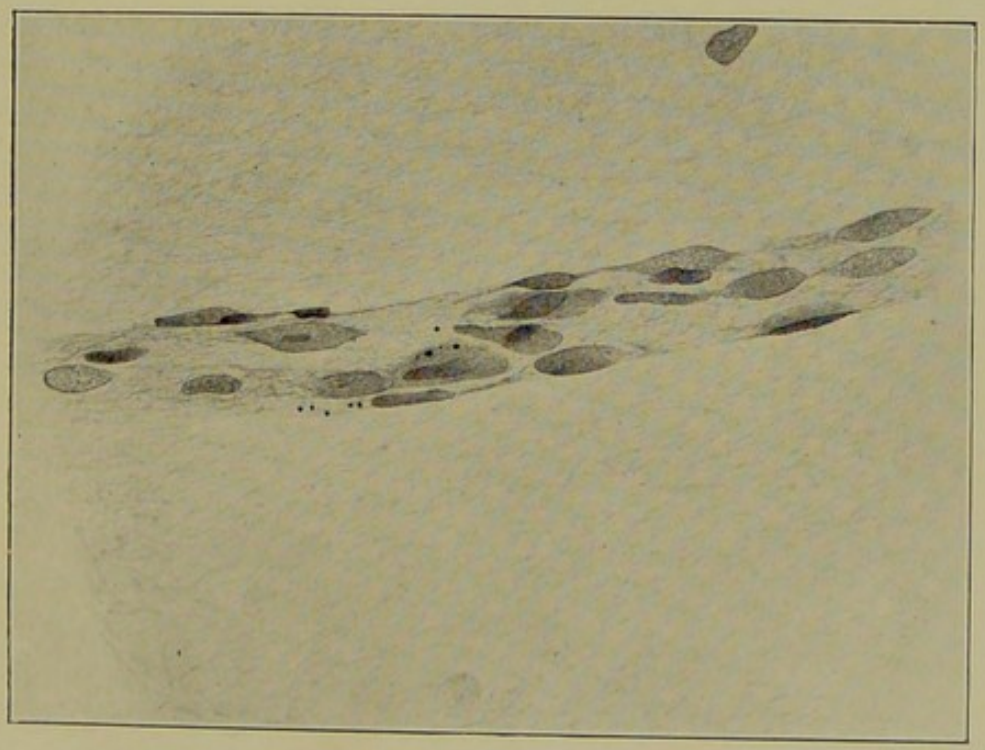


FIG. 53

A capillary blood-vessel in the motor cortex of the rabbit's brain—see preceding figure—showing diplococci in the endothelial cells

myocardium, pericardium, and nodules. If the process is acute the connective tissues swell; there is hyaline degeneration, and there may be necrosis. Where there are blood-vessels there is hyperæmia, and there may even be small hæmorrhages and thromboses. There is also fibrino-cellular exudation. The cardiac muscle fibres lose their striation and there may be well-marked fatty changes. There is connective tissue cell proliferation, and if the process has been severe and of long duration there is sclerosis spreading from the position of the small blood-vessels. Then we also know that the diplococci in the valves, pericardium, and nodules, are rapidly destroyed at the sites of the lesions, though it is probable that the poisons that are produced may linger after the disappearance of the organisms. But we are in ignorance as to the nature of any poisons that may be formed by the action of the diplococci.

If these observations are applied to the pathology of rheumatic chorea, we should expect to find that the lesions in chorea are various. In very acute and rapidly fatal cases we should expect hyperæmia, possibly small hæmorrhages, and foci of necrosis in the cerebral tissues; also minute emboli or thromboses in the terminal capillaries. In the less acute cases we should expect changes in the region of the minute blood capillaries, such as cell exudation and cell proliferation, and also degeneration of nerve cells. In the chronic cases we should expect perivascular fibrosis and small areas of sclerosis. There would probably be considerable difficulty in demonstrating the organisms, especially in the more chronic cases. On the other hand, it is quite possible in some cases that they may be present in such numbers that, escaping from the vessels into the brain tissue, they may set up sufficient swelling in the neighbourhood of these minute capillaries to cause their occlusion from pressure upon the delicate walls. On the other hand, our investigations throw no light upon the regional localisation of chorea, neither do they throw light upon the action of toxins or the characteristics of the brain itself, both most important factors in the pathology of chorea. It would, however, appear probable that the actual commencement of chorea in rheumatism is associated with the presence of the diplococci in the brain.

Up to this point we have contented ourselves with reasoning from our facts upon the pathology of chorea. It now remains

for us to allude to some of the numerous observations of other investigators upon this subject, which have, it is clear, guided us in arriving at these conclusions, and which are of the utmost importance in any investigation of such a nature as this one. In 1863 Dr. Kirkes,[1] noticing the constant presence of vegetations on the valves of the heart in fatal chorea, suggested that the disease might be caused by the irritation produced in the nerve centres by fine molecular particles of fibrin, which were set free from the inflamed endocardium and carried by the blood into the capillaries of those cavities. Dr. Hughlings Jackson,[2, 3] in 1864, wrote : " I think from many circumstances that embolism is a frequent cause of chorea. I do not say plugging of the trunk of the middle cerebral, but probably of some of its ramuscles which supply convolutions near to the corpus striatum." In 1865 Sir William Broadbent,[4] by an independent research, arrived at much the same conclusion as had Dr. Hughlings Jackson, and also laid stress upon the importance of alterations in the blood as a predisposing cause. Dr. H. M. Tuckwell,[5] in 1867, published a case of chorea in which the necropsy disclosed an extensive superficial softening of the convolutions, the result of embolism. And again, in the *St. Bartholomew's Hospital Reports* for 1869, he recorded another fatal case in which there was embolism of the right posterior cerebral artery, and figured in a plate both the mitral valve and the vessel that had been plugged. It is impossible to over-estimate the value of those researches, for they at once brought the subject into the field of controversy and put forward a hypothesis capable of proof or disproof.

The whole question of cerebral disease was further advanced by the experimental researches of Fitz, Hitzig, Ferrier, and others upon cerebral localisation. Later opponents arose to the embolic theory, Ogle, Barnes, Dickinson, Bristowe, and Bastian in particular advancing objections to this hypothesis. Dr. W. H. Dickinson,[6] in 1876, wrote thus upon this question : " We see in chorea a widely distributed hyperæmia of the nervous centres, not due to any mechanical mischance, but produced by causes mainly of two kinds—one a morbid, probably humoral influence which may affect the nervous centres as it affects other organs and tissues ; the other, irritation in some mode, usually mental, but sometimes what

is called reflex, which especially belongs to, and disturbs, the nervous system, and affects persons differently, according to the inherent mobility of their nature. The course of the disease is sufficiently traced in hyperæmia and its results." Dr. H. C. Bastian,[7] in 1877, in a paper entitled, "Remarks on the Pathology of Chorea," writes: "In common with many who have spoken with greatest authority on this subject, I look (certain rare cases excepted) to an altered and often anæmic blood state as its predisposing cause in individuals of a certain age and nervous temperament. Secondly, I look to the irritation in such individuals of a disturbed nutrition in the corpora striata and adjacent parts of the brain, tending to issue and often actually issuing, in what, for want of any more appropriate term, may be called a subacute inflammation of these centres—often characterised in part by the production of multiple minute thromboses." In 1876 Dr. Hughlings Jackson, after alluding to those cases of chorea in which Dr. Bastian found plugging due to thrombosis, writes: "It may be, I would admit here, that the hypothesis of embolism will be displaced by Bastian's hypothesis of thrombosis as an explanation of many cases of chorea." In a footnote to this paper he further writes: "Having regard to the great elaborateness of the movements in chorea, I still think it most probable that the convolutions are the parts diseased." Since the time of those papers numerous investigators in England and on the continent have proved beyond controversy that chorea and rheumatic fever are very frequently associated, so frequently, indeed, that some have thought that all chorea was the result in some way or another of rheumatism. As this association became certain, it was natural that the view that some poison (the result of the rheumatic state) was the actual cause of chorea should gain many adherents. A considerable amount of information has also been gained about the morbid anatomy of fatal chorea, though, as pointed out by Dr. Risien Russell[8] in his article upon Chorea in Professor Clifford Allbutt's "System," many of these investigations have not been sufficiently thorough. It is easy to understand the difficulty of such investigations when it is borne in mind that those who have undertaken them had but little to guide them as to what to look for, or where, in such a large organ as the brain, to look. It would appear nevertheless, that the more

careful the researches the more frequently have some definite morbid changes been discovered.[9] Hyperæmia appears to be common, as also softening from the effects of minute emboli.[10] Punctiform hæmorrhage and perivascular exudations have also been found.[11] The late Dr. Charlewood Turner[12] described cloudy swelling of the large pyramidal cells, and Dana[13] hyaline swelling of nerve cells and chronic lepto-meningitis.

Another result of the establishment of the association of rheumatic fever and chorea was the view that the changes in the brain were analogous to those which occur in the valves of the heart and in the subcutaneous nodules. To quote from the Harveian Lectures for 1888, by Dr. W. B. Cheadle :[14] "I may point to the possibility of some proliferative change in the neuroglia akin to that of the fibrous tissue elsewhere as a point which needs examination." If these local lesions in rheumatic fever be each one of them looked upon as an individual and complete rheumatic process, then we have the clinical expression of such a view as the above in the statement by Sir Dyce Duckworth,[15] that chorea is cerebral rheumatism, in support of which, in 1894, he read a paper in Rome at the International Congress of Medicine. Again, in a recent communication to us, Dr. Hughlings Jackson refers to the possibility that some of the changes in the brain are analogous to those found in the cardiac valves and subcutaneous nodules. On the other hand, the view that chorea was in most part the direct effect of rheumatic fever was opposed by such an authority as Sir William Gowers,[16] in his "Manual of Diseases of the Nervous System," in 1893. He admitted the frequency of association of the two, but writes : "The hypothesis which seems best to explain the facts is the old theory that the common cause of the endocarditis and the chorea is a blood state allied to, but not identical with, that which causes acute rheumatism." He considered that the facts suggested a toxic change of a chemical character rather than an organised virus.

One of the most recent researches upon the morbid anatomy of acute chorea is that of Dr. Bertram Abrahams.[17] The patient, aged 28, was pregnant ; there was a history of scarlet fever but not of rheumatic fever, and during life there was a systolic mitral murmur pointing to slight mitral endocarditis The illness lasted from April 25, 1899, to June 1. The moto

cortex showed changes, especially upon the right side in the region of the right parietal lobe. In this region there was a profuse exudation of small cells which were found to be uninuclear leucocytes. In some sections these cells could be traced passing through the walls of the small blood-vessels and outside the vessels occupied the peri-neuronal lymph spaces. There were haziness and swelling of the pyramidal cells. There was no trace of micro-organisms. Dr. Abrahams, in his comments, writes as follows : " I would venture, however, to submit that it tends to support the following general deductions. Firstly, the changes noted are sufficient to explain the clinical manifestations of the disease on the ground of disturbances in the cells of the so-called motor cortex. Secondly, their nature is such as to be susceptible of complete and rapid recovery—a fact in harmony with the description of the disease as functional. Thirdly, there is nothing in them inconsistent with the conception of chorea as an affection produced by a blood state—namely, the rheumatic toxæmia." With the development of bacteriology new facts were obtained, and during the last fifteen years the opinion that rheumatic fever was of microbic origin has steadily gained ground. This resulted in the recognition of the possibility that some bacterial poison might be the cause of rheumatic chorea, an idea strengthened by the analogy of the occurrence of diphtheritic paralysis as a result of the infection with the specific bacillus of diphtheria. But though the view that the condition might be the result of some poison circulating in the blood gained in force, there still, we believe, must be recognised the clinical fact that rheumatic chorea is often remarkably asymmetrical in its distribution, sometimes focal, and this, we think, militates against the theory of a diffuse poison being the only causal agent, and points rather to multiple local lesions being present in addition to the more diffuse cerebral toxæmia.

Finally, within the last ten years, various observers have isolated organisms from the brain and its pia mater in fatal chorea. The organisms most usually found have been cocci,[18] though Pianese,[19] in 1893, isolated a bacillus which produced convulsions in animals. In 1894, Dana[20] isolated a diplococcus from the meninges, and in 1898, Apert[21] isolated a diplococcus from the brain, and was of opinion that the organism was similar to that described by Triboulet[22] as a

cause of aggravated rheumatic fever. In 1899 Westphal Wassermann and Malkoff[23] isolated from the brain in a fatal case of chorea a diplococcus which produced fever and multiple arthritis in a series of eighty rabbits. This diplococcus Professor Wassermann considered to be the specific cause of rheumatic fever. In 1899, Maragliano,[24] as a result of his researches, considered chorea to be a cerebral infection by staphylococci, and maintained that the disease was due either to the presence of these organisms or to the poisons which they produced. In 1900 we produced chorea in a rabbit by the intravenous inoculation of a diplococcus, which we believe to be a cause of rheumatic fever,[25] and demonstrated the organisms in the pia mater and in the endothelial cells of the blood capillaries dipping into the cortex.

It remains for us to consider some of the clinical characteristics of rheumatic chorea and to attempt to explain them by the hypothesis that in most cases, possibly all, the commencement of the disease is the result of the actual presence of the diplococci, together with the poisons they produce in the brain. Any such considerations must be limited by our ignorance of the part taken in the disease by the brain itself, which fact is without doubt a very important one, and also by our ignorance of the exact action of the toxins that are produced by the organisms. The hypothesis involves the consideration of two morbid processes in the actual production of the disease—one, focal dependent upon the tissue changes in the regions where the diplococci are located, the other dependent upon the toxic effects of the poisons upon the nerve elements. How much is to be attributed to each factor will be made far more clear when these poisons can be isolated and studied by experiment.

The onset of chorea is usually gradual, some times acute, in rare cases almost sudden. In the acute cases it is reasonable to suppose that there is a considerable and rapid invasion of the brain by diplococci. It is possible that they escape from the vessels and set up swelling and exudation in the surrounding tissues, just as in the nodule they may rapidly give rise to a swelling which is perceptible to the eye. In cases of more gradual onset the invasion is probably less severe either in the intensity of virulence, or in the number of the organisms that gain access to the brain. The symptoms are sometimes

focal and sometimes general, and are dependent upon the factors mentioned above. The lesions that are produced usually resemble those represented by the nodules in the completeness of their recovery and also in their varying duration. This analogy must, however, not be pushed too far. We recognise that the cerebral processes are peculiar, for they are of such complexity that when disordered they are especially slow to return to normal, even though the actual cause of the disturbance may have been removed. Some rare cases are fatal, the intensity of the disease resembling then the severe types of rheumatic carditis. Other cases recover only partially, and for years a chronic condition of disordered movement persists. We should suspect that this points to some actual, though slight, multiple organic lesions, and in such cases, also, some peculiarity in the brain itself is highly probable. This view is supported by the pathological changes that have been found in that chronic progressive form of chorea known as Huntingdon's chorea. It was clearly demonstrated by the earliest investigators that the paralytic manifestations are the result of a more severe nerve lesion than are the inco-ordinate movements. These paralytic symptoms we would associate with local tissue changes in the regions invaded by the diplococci.

That only certain cases should develop chorea is remarkable and cannot as yet be explained, but it is only a further evidence of the specific action of the more complex poisons, the truth of which we have been led to recognise by the study of peripheral neuritis. There is little doubt, too, that in children more cases than are perhaps generally recognised present slight manifestations of chorea during acute rheumatism (a point which has been emphasised by Sir Thomas Barlow). Again, many others, without evidence of actual chorea, are highly nervous and excitable during an attack of rheumatic fever. That the disease should be common in children and rare in adults is in accord with many other acute infections; the child is less resistant to them than the adult, and the manifestations are more widespread.

The causal relation of fright to chorea is, and always has been, a great difficulty. Some authorities—for example, the late Dr. Sturges[26]—have attributed to fright and mental strain a most important position, others with equal ability

have opposed this view. The truth probably lies in the middle course. Many of the examples attributed to fright have, no doubt, only proved that the condition of the brain must have been very unstable, and the essential point has been, not the trivial cause of a fright, but this condition of instability. It is well known that rheumatic children are often highly nervous and excitable, and especially so before an attack of chorea; this fact has been insisted upon, among others, by Dr. J. F. Goodhart, Dr. W. B. Cheadle, and Sir Dyce Duckworth, and quite recently by Dr. G. F. Still. How much of this instability in any case of chorea is to be attributed to hereditary weakness and how much to latent rheumatic processes it is difficult to decide. At present the pathological processes that result from fright are unknown, though on the clinical side it is recognised that their effects may be as far reaching and of as long duration as morbid conditions produced by bacterial poisons. The association of fright and rheumatic chorea appears to stand at present thus. Rheumatism produces a cerebral state analogous to that produced by fright; what that condition is we do not know. When chorea arises in a *rheumatic* child and is attributed to fright, it would seem probable that the fright acted upon the rheumatic brain much as strain acts upon the rheumatic heart—namely, intensified the rheumatic process in the brain and precipitated chorea, as does strain hasten the onset of rheumatic carditis. Such a brain previous to the fright is unstable from rheumatic infection, and then the fright itself lowering still more the cerebral resistance, starts some times at once, sometimes after a short interval, the actual phenomena of chorea.

III. The Occurrence of the Diplococci in the Polymorphonuclear Leucocytes

By centrifugalising the pericardial exudate from a case of acute rheumatic pericarditis, we have succeeded in demonstrating the presence of these organisms in the polymorphonuclear leucocytes. In one instance there were as many as three pairs of diplococci in one leucocyte. In rabbits we have also demonstrated them in the same cells in the joint exudate. The fact that the diplococcus can be discovered in

the polymorphonuclear leucocytes is of interest because it is well known that there is a moderate leucocytosis in rheumatic fever. It is therefore possible that this leucocytosis is protective in function.

IV. The Incubation Period of Rheumatic Fever

It does not seem very probable from our observations that rheumatic fever has a definite incubation period. If it should so happen that a very considerable infection suddenly occurred, then the symptoms show themselves rapidly. Dr. A. E. Garrod[27] in his treatise gives several examples in which the local symptoms showed themselves on the second day or within the first week, and in these instances there was a very definite history of chill and cold. Rabbits intravenously inoculated usually show the first local lesions at the end of the second or the beginning of the third day. On the other hand, the resistance to the disease being great, it may well be in other instances that for some considerable time the infection is kept at bay and general indeterminate symptoms alone be manifested. Then one of two events may occur: either the resistance may prove effectual and the illness come to an end without having ever been recognised as rheumatic fever, or the infection may conquer and rheumatic fever result after a considerable period of previous ill-health. This occurrence of rheumatic fever after some weeks of previous malaise is thoroughly recognised by clinicians.

In the consideration of this question a study of the tonsils after death is of some interest. These are not uncommonly enlarged and very unhealthy at the time of death, and when sections are made through them scattered foci of inflammatory exudation may be discovered at some distance from the surface (a point insisted upon by Dr. William Hill[28] in 1889), the structure of the tonsil itself is indurated and points to a condition of subacute inflammation and disease of long standing. In such a condition as this we naturally wonder how great possibilities for harm exist in these scattered foci of active disease, to what extent the organisms may develop at these sites, and to what extent they may gain access to the system. The importance of this question has been still more accentuated

by the extensive researches of Fritz Meyer,[29] conducted in the laboratory of Professor von Leyden, and published in February 1901. Meyer, after an investigation extending over two years, succeeded in repeatedly isolating from the throat in rheumatic patients a diplococcus easily discolourised by Gram's method. This grew well on blood agar in staphylococcal masses, and in liquid media of high alkalescence in streptococcal chains, and produced in rabbits the same phenomena as did the diplococcus isolated by ourselves.

V. Is Fever a Primary Phenomenon in Rheumatic Fever, or is it Secondary to the occurrence of Local Lesions?

Upon this point we are able to bring forward some facts which suggest that fever may be a primary phenemenon of the disease. This view has been held by such authorities as Graves, Todd, Fuller, and others, while on the other hand, Besnier and Homolle considered the fever to be secondary to the local lesions. In the valuable monograph by Dr. A. E. Garrod upon rheumatism the evidence for and against these views and the difficulty there is in arriving at a solution of this question are stated with great clearness. As Dr. Garrod has written, "It is only from the presence of the local manifestations that it is possible to be sure of the nature of the attack." Experiment overcomes this difficulty in some measure, but at present not altogether, for we do not understand exactly the method of infection in rheumatic fever. Granting, for example, that the throat is an important site of infection, we cannot say precisely under what conditions the diplococci gain access to the system, though it is probable that the path is through the lymph channels.

The experimental method of intravenous inoculation is a gross method, for one considerable dose of the organisms is at once injected into the circulatory system and all resistance at the site of inoculation put out of court. Admitting this, it is clear that we can by this means state precisely when infection took place, and therefore can judge whether fever is a primary phenomenon or not *under those conditions*. We have found the temperature rise within twenty-four hours, whereas the local lesions usually do not appear until the third

day. In one case pericardial fluid from a case of rheumatic pericarditis was removed in sterilised pipettes four hours after death, and then incubated for twenty-four hours. The fluid contained the diplococci in great numbers. This was intravenously inoculated, and four hours afterwards the temperature had risen to 105°—a more pronounced rise of temperature than occurred when cultures upon blood agar were used. This result suggests that toxins in the pericardial fluid might have assisted in causing this rapid rise of temperature.

VI. The Experimental Production of Morbus Cordis

Whatever views may be held by others regarding the relation of this organism to rheumatic fever, there can be no possible doubt that it is capable of producing cardiac lesions with great constancy. We have repeatedly observed the occurrence. The mitral, tricuspid, and aortic valves have all been affected, and, in addition, dilatation of the heart with fatty change in the myocardium and pericarditis has occurred. These results are extremely suggestive of the true meaning of the infection. It seems highly probable, too, that the study of heart disease may be simplified and be made more certain by observations upon the conditions experimentally produced. There is one aspect of this subject which has a very important bearing upon the study of rheumatism, and that is the involvement of the right side of the heart. It is repeatedly stated that the right side of the heart is but rarely affected in rheumatic fever, and so frequently is this statement made that we believe it may lead to error. Sir Thomas Barlow, among others, has, to our knowledge, frequently pointed out that several valves are usually injured in the severe rheumatic carditis of childhood, and in such cases we believe, with others, that it is comparatively common for the tricuspid valve to be affected. The lesions are less severe, no doubt, often indeed very slight, but they are frequently present. Again, when it is remembered that the tendency of these lesions in rheumatism is towards recovery, it may well be that a thickening of the tricuspid segments, in reality of previous rheumatic origin, may be ascribed entirely, rather than in part, to mechanical

overstrain the result of some advanced lesion upon the left side. The question, as it presents itself in rheumatic fever, is one of degree, and to argue that an affection of the right side of the heart, even if severe, *cannot* be rheumatic, but is due to a secondary infection, is, we believe, to assume more than can be granted. When the extremely delicate valves of the rabbit's heart are affected, the granulations are minute and the distinction between the affection of the valves on the right and on the left side less evident. The aortic segment of the mitral is, however, as in man a less delicate structure, and it is in that segment that we have noted in addition to granulations some thickening and opacity. It is possible, therefore, that the preponderance of the mitral disease in rheumatism is in part dependent upon the more elaborate structure of that valve. It is quite possible that by the experimental method the solution of certain other difficulties will be obtained, for just as in man the mitral valves or the aortic may be apparently alone affected, so in rabbits we have observed the same occurrence ; yet even in those cases in which only one valve apparently is affected it is quite possible that more than one was infected, but that these others have by virtue of the phagocytic action of their connective tissue-cells, destroyed the invading organisms which attacked them in comparatively small numbers.

At the risk of repetition we would once more state that injury to the tricuspid valve in the severe rheumatic carditis of childhood, though slight in extent, is frequent in its occurrence, and the more carefully it is looked for the more frequently it will be found to occur. That, if rheumatic fever is a disease due to an infection, there is danger in the assumption that disease of the tricuspid valve in a rheumatic patient is necessarily due to a secondary infection. That such may be the case is certain, but how often it is the case yet remains to be proved. Again, when a patient who has been the victim of repeated rheumatic attacks dies from malignant endocarditis, it is quite as legitimate to assume that the condition is truly rheumatic, though altered in type, as it is to assume the occurrence of some secondary infection. If the organisms are isolated from the valve and demonstrated as specific yet not rheumatic, then the position is clear, but to judge by the size of granulations, by the rupture of chordæ tendineæ, by

the spread of the vegetations on to the surface of the auricle, or by the marked affection of the tricuspid valve, is, we believe, dangerous and liable to result in an attempt to limit a disease which is perhaps of all diseases one of the most variable. This fact we can state, that we have succeeded in isolating a diplococcus from cases of malignant endocarditis in which rheumatism appeared to be the only cause, and have reproduced in animals, even to the very identical valves, a malignant endocarditis, and then later a condition indistinguishable, as far as the arthritis and endocarditis are concerned, from that produced by the diplococcus of simple rheumatism. Clinical observation has also demonstrated that no line can be drawn between simple rheumatic endocarditis and the malignant types as observed in man.

The occurrence of ante-mortem thrombosis in the heart in rheumatic fever. The causes of its occurrences are probably various—there are the mechanical difficulties associated with the endocarditis, there is the weakness of the heart wall, and the increased tendency of the blood to clot. In rabbits the stages of the process can be studied. In one case we noted rapid, feeble, distant heart sounds and the development of a systolic murmur, audible at the lower angle of the right scapula. We were puzzled by the murmur, and suspected, from the condition of the heart, pericarditis. The necropsy showed no gross valvular disease, but a large ante-mortem clot in the right auricle. It is clear that in this case one factor in the causation of ante-mortem thrombosis could be excluded —namely the mechanical one due to advanced valvular disease. The next case in which we noted the feeble, distant heart sounds we did not wait, but after assuring ourselves that it was not a passing phenomenon the animal was killed and the heart examined. Ante-mortem thrombosis had commenced in the left ventricle in the neighbourhood of the valve ring beneath the mitral cusps and at the apex of the left ventricle. There was no gross valvular lesion. Finally, just as in man a mitral systolic murmur may appear early in the illness and then rapidly disappear, so in rabbits we have observed the same phenomenon and have ascribed it to the same cause—namely, to an acute dilatation of the ventricle rather than to an organic affection of the mitral valve.

REFERENCES

[1] "New Sydenham Society's Year-book," 1863, Summary by Dr. Handfield-Jones.

[2] *London Hospital Reports*, 1864, vol. i, p. 459; *Lancet*, November 26, 1864, p. 606.

[3] "Note on the 'Embolic' Theory of Chorea," *Brit. Med. Jour.*, December 23, 1876.

[4] *Brit. Med. Jour.*, vol. i, 1865.

[5] *British and Foreign Medical and Chirurgical Review*, p. 506; *St. Bartholomew's Hospital Reports*, vol. v.

[6] *Transactions of the Royal Medical and Chirurgical Society*, 1876.

[7] Bastian, "Remarks on the Pathology of Chorea," *Brit. Med. Jour.*, January 13 and 20, 1877.

[8] Chorea, "System of Medicine," Albutt, vol. vii.

[9] Raymond, *Bulletin Medical, Paris*, 1896, vol. x.

[10] "Pathological Anatomy of Chorea," *Brain*, 1890.

[11] *Ibid.*

[12] *Transactions of the Pathological Society of London*, 1892, vol. xliii.

[13] *American Journal of Medical Science*, 1894, p. 31.

[14] "Manifestations of the Rheumatic State," Harveian Lectures. 1888.

[15] Atti dell' XI. Congresso Medico Internazionale, Rome, 1894, vol. iii.

[16] "Manual of Diseases of the Nervous System," 1893, p. 854.

[17] "Cortical Changes in Acute Chorea," *Transactions of the Pathological Society*, 1900.

[18] Chorea, "System of Medicine" (Allbutt), vol. vii.

[19] *La Natura infettura della Corea del Sydenham*, Napoli, 1893.

[20] "The Microbic Origin of Chorea," *American Journal of the Medical Sciences*, 1894, p. 31.

[21] *Comptes Rendus de la Société de Biologie*, Paris, 1898, vol. v, p. 128.

[22] *Ibid.* 1898, vol. v, p. 214.

[23] *Berliner Klinische Wochenschrift*, 1899, No. 29, p. 638.

[24] *Centralblatt für Innere Medicin*, 1899, Band XX, p. 489.

[25] *Transactions of the Pathological Society*, October 1900.

[26] The *Lancet*, September 29, 1888, p. 605.

[27] "A Treatise on Rheumatism."

[28] "Tonsillitis in Rheumatic States."

[29] A Paper read before the Society for Innere Medicin, Berlin, 1901.

PAPER NO. XV

A CONTRIBUTION TO THE STUDY OF MALIGNANT ENDOCARDITIS

(From vol. 85 of the *Medico-Chirurgical Transactions*.)

This paper was the result of some years of investigation, and is concerned with the difficult problem of the relation of malignant endocarditis to simple rheumatic endocarditis—clearly a question of the greatest practical importance in general medicine, and one realised by all who are alive to the great frequency of rheumatic heart disease. The relation of the two processes was brought at once into prominence when the infective nature of acute rheumatism was determined, for it compelled us to picture the possible results of such an infection when it was located in a valve. The two essential questions to be answered are: Is it probable or even possible that the rheumatic infection, belonging as it does to the group of streptococci, will produce valvular lesions that will always run a benign course? Secondly, if they do not, what result will follow? The solution offered here, which may be studied more fully by the light of our later paper, No. XXIII, is that acute rheumatic endocarditis may show all grades of virulence and may in itself, without any added infection, be a cause of malignant endocarditis. This statement does not imply that all malignant endocarditis is rheumatic in origin or that on occasions some other infection may not cause a malignant endocarditis in a patient who has previously suffered from a rheumatic endocarditis.

In 1903 *Dr. Ainley Walker and Dr. Beaton published an important contribution to the bacteriology of acute rheumatism which supported our investigations.*

I. Introductory Outline

(A) *A Group of Cases of Malignant Endocarditis closely associated with Rheumatic Fever*

While investigating the pathogenesis of rheumatic fever, our attention has been directed to certain cases of progressive heart disease which run a more or less prolonged course, and

terminate almost invariably in death. After death it is found that the valves of the heart are very extensively diseased, and that the morbid process is often extremely active. Among such cases there is one group in which we were particularly interested, for previous to the fatal illness there had been a history of rheumatic fever ; sometimes there had been repeated attacks, and during the last illness symptoms had arisen which suggested that rheumatism of some unusual type was in reality the true excitant. The symptoms in these cases arose insidiously, and there was no local focus of suppuration, no wound or other demonstrable cause which may be considered to have been the starting-point of this progressive form of heart disease. This class of case is well recognised, for it is a comparatively common one in the large hospitals. It is possible in some instances to detect the nature of the disease even early in the illness, because of the persistently excited action of the heart and loudness of a systolic murmur ; but, on the other hand, even when death has occurred, several observers of equal acumen, and with the same advantages in the study of the case, may differ in their opinion as to whether the condition is one of rheumatic morbus cordis or so-called "infective endocarditis." No doubt the great majority of these cases as they progress diverge more and more from the appearance of rheumatic fever, and the force of the disease falls so exclusively upon the cardiac valves that it may be difficult in the end to detect any clinical resemblance ; but it is equally certain that the more these cases are carefully studied, the more difficult it is to say where a distinctive line can be drawn between them and acute rheumatism. Anæmia, prostration, wasting, pyrexia, and infarction are very frequent and important symptoms in this disease, but there is not one of these which may not occur, to a lesser degree, in severe rheumatic fever. In these cases, again, suppuration does not occur even in the blood-clot of the aneurysms that may result, but numerous white infarcts are often found in the kidneys, lungs, or spleen after death.

(B) *"Malignant" Preferable to "Infective" as a Title for this Form of Endocarditis*

The usual procedure in this country is to describe such cases as examples of "infective endocarditis," and if by

this term no suggestion were implied that rheumatic endocarditis was non-infective, the description would be an excellent one. It is unfortunate that such is not the case, but that through no fault in the term itself the name in question has been widely used in *contradistinction* to rheumatic endocarditis; and this is the more strange because for several years rheumatic fever has, in spite of the absence of actual proof, been looked upon as due to an infection.

For this condition the name malignant endocarditis seems to us preferable, for whether it proves fatal or not, the type is malignant.

(C) *Researches of other Investigators upon Malignant Endocarditis*

An immense amount of research has been devoted to the study of malignant endocarditis, and it would be impossible in such a paper as this to mention the names of the many investigators. Their results have been of far-reaching importance. They have definitely settled the microbic origin of the condition. They have also shown that various microorganisms may give rise to malignant endocarditis, but that the most usual cause is a streptococcus. Experiments upon animals have resulted in the reproduction of the disease, though not with constancy, and in some cases the cardiac valves have been damaged mechanically before endocarditis has resulted. It may be justly asserted that these investigators have elucidated the broad outlines of the pathology of malignant endocarditis, though there are several difficult problems yet to be solved, among which is the relation of such cases to rheumatic fever.

(D) *Renewed Investigation of Malignant Endocarditis Desirable*

Heretofore it has not been possible to solve this problem, for there has been no agreement upon the cause of rheumatic fever. The outcome of this limitation of knowledge has been the widespread belief that malignant endocarditis in a rheumatic patient is invariably a result of some secondary infection of the tissues injured by previous rheumatism. Nevertheless there have been some clinicians and pathologists who have

felt this attitude to be too rigid, and have, without the means of bringing forward complete proof, believed that some cases are truly rheumatic in origin. At the present time so much evidence has been obtained in favour of rheumatic fever being the result of a diplococcus infection, that it seems a proper occasion to investigate once more this question of the relation of the two diseases.

(E) *The Result of the Authors' Investigations*

It is this investigation with which our paper is concerned, and our conclusion can be shortly stated thus : *That there is a group of cases of malignant endocarditis which is rheumatic in nature.* How comprehensive this group will prove to be further investigations alone can decide.

Before we summarise the reasons for this conclusion we are anxious to make clear the scope of our paper. We do not claim that the view that rheumatic fever is a cause of malignant endocarditis is an original one ; we are well aware that others—as, for example, Ogle, Osler, Peter, Burkart, and Fernet—have entertained this opinion ; that others before us have demonstrated that organisms similar in their morphology may occur in the two diseases, and have felt that in some instances no clinical distinctions can be drawn between simple and malignant endocarditis. Our paper, as its title claims, is but a contribution to the study of malignant endocarditis, and affords, we believe, a strong support of the view that malignant endocarditis may be of rheumatic origin.

(F) *Reasons for the Assertion that there is a Malignant Rheumatic Endocarditis*

The chief reasons upon which we rely for support of our assertion can be summarised thus :

Firstly. The probability that some of these cases are rheumatic is in accord with clinical experience.

The clinical cases we record will bear out this statement.

Secondly. The probability that some of these are rheumatic is in accord with pathological experience.

The minute investigation of the morbid anatomy of the clinical cases we record supports this conclusion.

Thirdly. The probability that some of these cases are

rheumatic is in our opinion in accord with bacteriological experience, for—

1. A diplococcus is a cause of rheumatic fever.

2. A diplococcus can be isolated in pure culture from these cases of malignant endocarditis, which will reproduce the disease in rabbits.

3. The culture and morphological characteristics of these two diplococci resemble one another so closely as to lead to the conclusion that they are identical organisms.

4. The *Diplococcus rheumaticus* will produce malignant endocarditis, indistinguishable from that produced by the diplococcus isolated from certain cases of malignant endocarditis in man.

5. The *Diplococcus rheumaticus* may produce in a rabbit first a recoverable illness with the manifestations of rheumatic fever, and then on a second inoculation malignant endocarditis.

6. A diplococcus isolated from certain cases of malignant endocarditis in man will produce not only malignant endocarditis in rabbits, but a condition indistinguishable from the disease we believe to be rheumatic fever.

7. By these diplococci, every grade of endocarditis from simple to malignant, and from malignant to simple, can be produced, as our macroscopic specimens bear witness.

II. The Investigation

(A) *Clinical, Experimental, and Pathological Observations*

The first case will make clear the type we are studying.

Case 1. A child, aged 11, was admitted to St. Mary's Hospital, under the care of Dr. W. B. Cheadle, upon October 22, 1897, and died November 12. When three and a half years of age he had suffered from rheumatic fever, and when five and a half from scarlet fever. His mother had suffered from rheumatic fever. Five weeks before admission there had been swelling of the knees and ankles, and for five months there had been complaints of obscure pains in the chest and abdomen. There was no history of an injury, no suppurating focus, and no obvious cause which could be looked upon as an explanation of some secondary infection. Upon admission the boy was very anæmic, the temperature

was 100.8° F., pulse 100, respirations 28. The heart was much enlarged, there was a loud systolic mitral murmur, and also an aortic systolic murmur. The liver and spleen were enlarged, the urine was natural. Soon after admission crepitations were heard at the base of the left lung posteriorly, and there was pain in the left side.

Upon October 28 blood and albumen were found in the urine, and until death upon November 12 there was irregular pyrexia. Hæmaturia became persistent, and casts were found in the urine. There was pain over the spleen, and progressive enlargement of that organ. Purpura, vomiting, progressive anæmia, emaciation, and sweating were prominent symptoms, and finally the pulse became irregular and intermittent, and death resulted from cardiac failure.

The necropsy showed recent pericarditis, with two ounces of fluid in the pericardium, which contained a few flakes. There was extensive ulceration of both flaps of the mitral valve, and exuberant granulations spread over the surface of the auricle. The valves upon the right side of the heart were not affected; the heart itself was hypertrophied and dilated. There were numerous white infarcts in the spleen, with perisplenitis; it was soft, and weighed five ounces. There were numerous white infarcts in the kidneys, but none found in the lungs. Numerous subserous hæmorrhages were visible along the intestines. There were no abscesses, but many white infarcts, as already stated. Numerous micrococci were found in the granulations.

We admit that secondary infections can occur during life without any demonstrable cause, but it seems to us legitimate to argue upon such a case as this in the following way: Rheumatic fever is a bacterial disease, and one which apparently does not confer immunity. Evidence at present points to it as the result of a diplococcic infection, and it would appear that the diplococcus may exist for long periods in the body.

In such a case as the above there was a family and personal history of rheumatism, and such a child, as all clinical experience has shown, may be justly termed rheumatic. If, then, from such a case a diplococcus be isolated, it is as legitimate to assume that it may be the *Diplococcus rheumaticus*, under some unusual conditions, as to assume a secondary infection. The proof must rest upon an accurate study of the micro-

organism which is isolated, by various methods, including among these the method of experiment.

CASE 2. The next case was that of a woman aged 50, who was admitted to St. Mary's Hospital, under Dr. W. B. Cheadle, in June 1898, for dyspnœa of some months' duration. The only cause that was given for this dyspnœa was an attack of rheumatic fever eight years previously. Upon admission she was cyanosed and short of breath, and complained of pain in the left side. There was orthopnœa. The temperature was 102.8° F., pulse 103, respiration 40. The heart was much enlarged, and there was a mitral systolic murmur. The hands were deformed by previous attacks of rheumatism. The nature of the case remained quite in doubt, though towards the end irregular pyrexia, infarctions in the lungs and spleen, and purpura suggested the diagnosis of malignant endocarditis.

The necropsy showed recent pericarditis, adhesive in type, and also old adhesions, the result of a previous attack.

The mitral, tricuspid, and aortic valves showed extensive vegetative endocarditis, and there were vegetations over the surface of the left auricle. There were white infarcts in the lungs and spleen, but none in the kidneys. There was no suppuration. Numerous micrococci were visible in the granulations.

The necropsy disclosed characteristic malignant endocarditis, yet clinically this case was most obscure, and resembled at first a severe rheumatic morbus cordis. It was not until the end of the illness that the malignant character of the disease became apparent.

CASE 3. A patient aged 16 was admitted into St. Mary's Hospital in January 1900 under Dr. Lees, suffering from morbus cordis. When six years of age he had an attack of rheumatic fever, and since that time had suffered from three more definite attacks. His mother had suffered from rheumatic fever. The final illness had commenced insidiously, with pain round the heart, and three weeks before admission there had been pains in the ankles and knees. No cause was assigned for this illness, and on special inquiry of the mother she volunteered that she had thought this was another attack of rheumatism, because it commenced just as the previous attacks had done.

On admission the patient was very anæmic and wasted,

and there was irregular pyrexia, with well-marked mitral and probably aortic disease.

The course of the illness was progressive and malignant in type. Irregular fever, enlargement of the spleen, and hæmaturia, with progressive anæmia and emaciation, were the prominent symptoms, and throughout the time that the patient was in the hospital no doubt was entertained as to the nature of the illness.

The necropsy showed a few ounces of clear fluid in the pericardium; the mitral valve was fringed with numerous vegetations, varying in size from a pin's head to a pea. There were recent vegetations upon the aortic valve, but the right side of the heart was unaffected. In the spleen there were three white infarcts, and in the left kidney one.

There was no suppuration.

This case was, in one respect, the converse of the preceding. The clinical diagnosis was quite definite, but the necropsy showed a condition which, without the clinical history for a guide, could have been explained as active rheumatic morbus cordis, and not as malignant endocarditis.

We investigated the bacteriology of this case, and at first intended to include it (the resemblance was so striking) among our first series of cases of rheumatic fever published in the *Lancet* in September 1900; but we finally concluded, before publication, that it was better to exclude a border-line case of this kind, and have not made allusion to it until the present paper.

The bacteriological investigations resulted as follows:

Numerous diplococci growing in chains were demonstrated in films made from the granulations on the mitral valve, and cultures were made with the following media: agar, ascitic fluid, acid and alkaline bouillon slightly acidified with lactic acid. The liquid media were incubated both aerobically and anaerobically.

Twenty-four hours afterwards the results were as follows:

Upon agar, a poor growth of minute discrete colonies consisting of extremely minute diplococci. The pork medium and ascitic fluid were sterile. The alkaline bouillon showed a very poor growth of minute diplococci.

The acid milk, both aerobically and anaerobically, showed

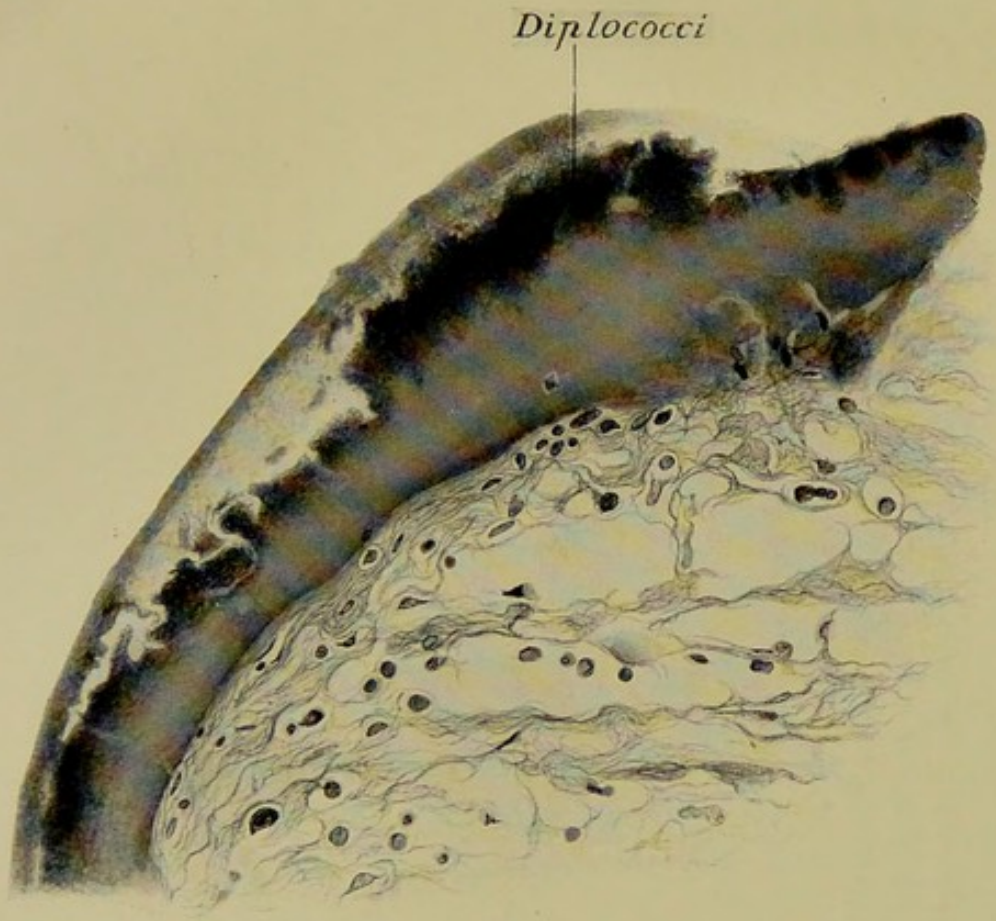


FIG. 54

Section through necrotic tissue of a vegetation upon the mitral valve (human), showing a dark fringe of deeply stained masses of diplococci. (Low power.)

FIG. 55

Section through the necrotic tissue of the same vegetation as the preceding under high magnification, showing vast numbers of the diplococci. (Zeiss, obj. $\frac{1}{12}$, oc. 3.). *Cf.* Fig. 61.

a vigorous growth of diplococci in chains. This diplococcus was grown in the milk medium by means of sub-cultures for two months. From the original tubes a sub-culture was made upon blood-agar, and upon two occasions the contents of one blood-agar tube was injected into the auricular vein of a rabbit. The result in each case was negative.

The isolation of a minute diplococcus from a case such as this is in accord with the experience of Professor Litten,[1] who also isolated a minute diplococcus from a condition which he termed the malignant non-septic form of rheumatic endocarditis. Such cases as these he considered to be characterised by pyrexia, infarction, pallor, and sweating, with hæmaturia and enlargement of the spleen, but no suppuration.

Professor Litten was inclined to the view that this diplococcus was probably not identical with the diplococcus described by Professor Wassermann[2] as the cause of rheumatic fever. We believe that the diplococcus we isolated in this case is identical with the diplococcus which we have now isolated from twenty cases of rheumatic fever.

Case 4. This fourth case, although a case of rheumatic fever, we mention here because it resembled malignant endocarditis in this respect, that during life upon two occasions diplococci growing in chains were isolated from the blood. The patient was under the care of Dr. D. B. Lees, and the case is described in Paper No. VII. We naturally thought at that time that the case was one of malignant septic endocarditis, because we isolated streptococci from the blood during life, though previous investigations had made us somewhat doubtful of the validity of this conclusion. The clinical history, the course and character of the disease, and the result of the necropsy proved conclusively that it was a case of severe rheumatic fever. Though a most severe case of rheumatic fever with numerous and severe *local* lesions there was no suppuration, and yet during life there was a streptococcus, or, to be more exact, a diplococcus which grew in chains, circulating in the blood stream.

Case 5. A boy aged 10 was admitted to St. Mary's Hospital in April 1900, for heart disease, under the care of Dr. W. B. Cheadle. Six weeks before admission he had suffered from pain over the heart, sweating, and attacks of diarrhœa. A year previous to this he had been in the hospital for an attack

of rheumatic fever, and one brother had also suffered from rheumatic fever. On admission aortic and mitral endocarditis were discovered, and a very noticeable feature was extensive muscular wasting.

Upon April 30 he developed pericarditis.

In May there was arthritis, the ankles and knees being affected. There were also diarrhœa and vomiting. In June crepitations were detected in the lungs. In July infarction, sweating, and wasting were prominent, and death occurred in July, after eighty-eight days of irregular pyrexia.

This appeared to us during life to be a classical case of rheumatic malignant endocarditis.

There was unfortunately no opportunity of obtaining a complete necropsy, but the heart was removed, and the pericardium was found generally adherent. The heart itself was very little enlarged, but upon the mitral and aortic valves and on the wall of the left auricle there were extensive and exuberant granulations. The right side was not affected. Films from the vegetations showed minute diplococci in chains. Aerobic cultures in the milk medium were obtained and transferred to blood agar. A series of important experimental results followed.

The growth from six tubes was intravenously injected into a rabbit on July 28, and upon July 31 and August 1 the left knee-joint and left shoulder-joint were swollen. The animal died suddenly upon the fifth day. The necropsy showed exuberant granulations upon identical valves, namely the aortic and mitral. The micro-organisms were demonstrated in great numbers in the damaged valves.

In thus reproducing malignant endocarditis without any previous injury to the cardiac valves, we confirmed the classical investigations of Dreschfeld, Ribbert, Bonomé, Roux, Mannaberg, and others. It will also be apparent that in the course of this investigation we have confirmed the results of other observers by the experimental production of infarction and hæmorrhages.

Upon August 8 a second inoculation, from a culture obtained from this rabbit, was made into a smaller animal. Death occurred upon the fifth day from vegetative aortic endocarditis. No other valve was affected.

The cultures from this rabbit were contaminated with the

Bacillus coli, so recourse was had to the original culture, and a third inoculation made with a smaller quantity of the organism.

Death occurred on the nineteenth day. There was arthritis of the right knee and diarrhœa, but no clinical evidence of endocarditis or pericarditis. Death occurred from gradual cardiac failure due to dilatation and fatty degeneration of the heart muscle with ante-mortem thrombosis. In this case it will be observed there was no manifestation of malignant endocarditis, but the necropsy showed a simple endocarditis.

A larger quantity of the original culture was used for a fourth injection.

Death occurred on the tenth day. During life there were noted diarrhœa, heart disease, and arthritis of the right shoulder-joint. The necropsy showed well-marked malignant mitral endocarditis, white infarcts in both kidneys and in the spleen, but no pericarditis.

A smaller quantity of the original culture was injected into a fifth rabbit, which was killed—for it was moribund—upon the tenth day. During life diarrhœa, pericarditis, and arthritis were noted.

The necropsy confirmed that this condition was one of rheumatic fever.

The culture from this case was injected into a sixth rabbit, and death occurred upon the tenth day. There was arthritis, but no valvulitis. The heart's action was, however, extremely rapid, and for some days there was a mitral systolic murmur.

It is evident from this series of inoculations that in three instances definite malignant endocarditis resulted, in two death occurred from cardiac failure—without malignant endocarditis—and in one case death occurred from pericarditis.

Arthritis was frequent. One symptom occurred which we had not noticed in rabbits inoculated with the *Diplococcus rheumaticus* from rheumatic fever, namely diarrhœa; and this we know occurs not infrequently in man during the course of malignant endocarditis, and was a prominent symptom in the case from which this organism was isolated.

Case 6. A boy aged 13 was admitted into St. Mary's Hospital, November 1900, for morbus cordis, under the

care of Dr. Lees. Six years before he had suffered from enteric fever, and three years before from pneumonia and rheumatic fever. He had been ailing for two months previous to admission, and had suffered from pains in the chest and abdomen. The boy was pale and sallow, but well nourished ; there was mitral and aortic disease, and an enlarged spleen. He remained in the hospital until his death in January, and during that time there was usually irregular pyrexia, though sometimes for days the temperature remained normal. Death was sudden.

The necropsy showed general pericardial adhesion, and fungating masses of vegetation upon the mitral and aortic valves. There were petechiæ under the capsule of the liver. The spleen weighed fifteen ounces, was tough in consistence, and contained one recent infarct. There were numerous small hæmorrhages in the cortices of both kidneys. There was no suppuration. Two hours after death the mitral valve was exposed, and four tubes of the acid milk medium inoculated with fragments of the granulations. In two out of four there was a pure growth of very small diplococci growing in chains. Two were sterile.

Upon January 24 the growth from six small tubes was injected into a rabbit at 1 noon.

At 3 o'clock the temperature had risen to 105.2°, and a blowing systolic murmur was audible.

During the rest of January the temperature was raised, there was some diarrhœa, and the heart was rapid.

During February there was improvement, but occasional fever.

During March improvement continued.

Upon April 8 the hind limbs were found completely paralysed, and there was complete incontinence and loss of tone of the anal sphincter. The diplococci were isolated from the urine and the animal was killed. There was no definite endocarditis or pericarditis, and nothing to be found in the other viscera of importance except a hæmorrhage into the pia mater some quarter of an inch in vertical extent immediately above the lumbar enlargement.

It will be noticed that whether because the resistance of the animal was unusually great, or the initial inoculation not sufficient, the disease was not reproduced ; but the length

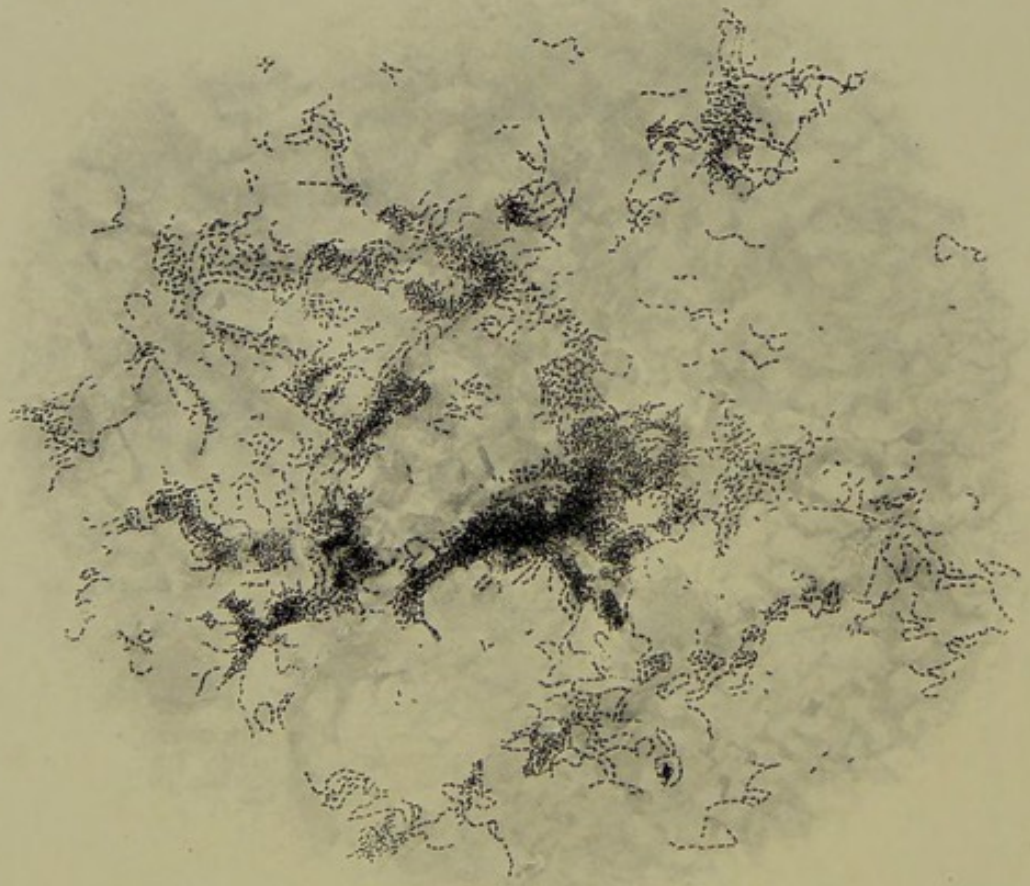


FIG. 56

The *Diplococcus rheumaticus* isolated from the valve in a case of rheumatic malignant endocarditis, growing in the acid-milk and bouillon medium in streptococcal form.

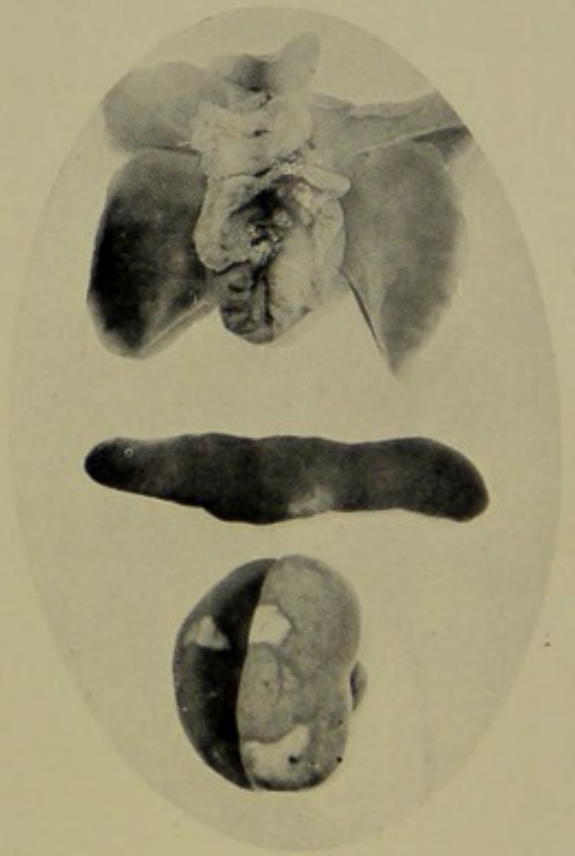


FIG. 57

The heart and lungs, the spleen and kidney of a rabbit dead of malignant endocarditis produced by the diplococcus. Exuberant vegetations are seen on the mitral valve and white infarcts in the spleen and kidneys.

of time (ten weeks) that the diplococci remained active in the body is a point of much interest.

Another inoculation from the original culture was made upon January 25, a day after the former inoculation, into a rabbit of smaller size. The animal was killed upon the tenth day; during life there were pyrexia and morbus cordis.

The necropsy showed well-marked vegetative mitral endocarditis, petechiæ in the heart wall, a white infarct which was softening in the left kidney, also white infarcts in the right kidney and spleen.

A pure growth of the diplococcus was obtained from the blood in the heart.

The third rabbit was inoculated from a culture from the preceding, and died in the night of the third day. The heart throughout the illness was extremely excited.

The necropsy showed the nearest approach to septicæmia we have seen with this diplococcus. Except for a minute granulation upon the aortic flap of the mitral and early peritonitis, there was no local lesion to be seen. Numerous diplococci were present in the granulation. There was excess of fluid in the pericardium, and numerous diplococci were present in the pericardial tissues.

The liver was pale; the kidneys pale; the spleen large, soft, and dark. The lungs showed no definite changes.

A fourth rabbit was inoculated with a culture from the preceding, and death ensued upon the sixth day. The necropsy showed pericarditis, with a fibrino-cellular exudation; slight mitral endocarditis, a small white infarct in the left kidney, and some perisplenitis—a condition of rheumatic fever.

A fifth rabbit was inoculated with a culture from the fourth, and died on the fourteenth day of severe pericarditis. The necropsy showed general recent pericardial adhesion, and a condition which resembled the severe general plastic pericarditis in the rheumatic fever of childhood.

There was no endocarditis.

Thus again it will be seen that both malignant endocarditis and a condition, we believe, indistinguishable from rheumatic fever had been produced by inoculations of this diplococcus.

This concludes our clinical investigations, though we would emphasise the fact that in some of these cases of malignant

endocarditis in rheumatic subjects rigors may occur for many weeks, yet after death not a trace of suppuration be found, and infarcts be discovered to be cicatrising. We have also obtained from post-mortem records thirty cases of malignant endocarditis without the mention of an abscess in any one, and all of them giving a previous history of rheumatic fever.

The next experiment illustrates that a culture originally obtained from a case of rheumatic fever may produce the malignant type of endocarditis after it has been passed through thirteen rabbits.

In June 1901 an intravenous injection was made into a rabbit from a culture which was the direct descendant of the original one obtained from the pericardial fluid of a fatal case of rheumatic fever in March 1900.

A very loud mitral murmur developed upon the seventh day, and the animal died upon the eighth. The necropsy showed that there was a large fungating vegetation upon the mitral valve, with white infarcts in the kidneys and spleen and one small one on the liver. The condition was one of characteristic malignant endocarditis.

The next experiment proves that a rabbit may survive a first inoculation with the diplococcus of rheumatic fever, recover completely, except for a slight thickening of the mitral valve, and then may die from malignant endocarditis, the result of a second inoculation.

The first injection was made from a culture of the diplococcus obtained from a boy suffering from acute rheumatic pericarditis. Treatment had necessitated a venesection, and the organism was isolated from the blood of the living patient.

The injection was made upon March 27, 1900, and four days afterwards there was arthritis of the right knee-joint. Later the animal became thinner and irritable, both knee-joints were affected, and the heart sounds were very rapid and weak. In May recovery commenced, and eventually the animal regained health.

Six months after recovery from the previous illness the second inoculation was made, upon January 30, 1901. The culture used was from the pericardial exudation of a fatal case of rheumatic pericarditis. The original growth had been obtained in the pericardial fluid itself in March 1900. This organism had repeatedly caused rheumatic fever in rabbits,

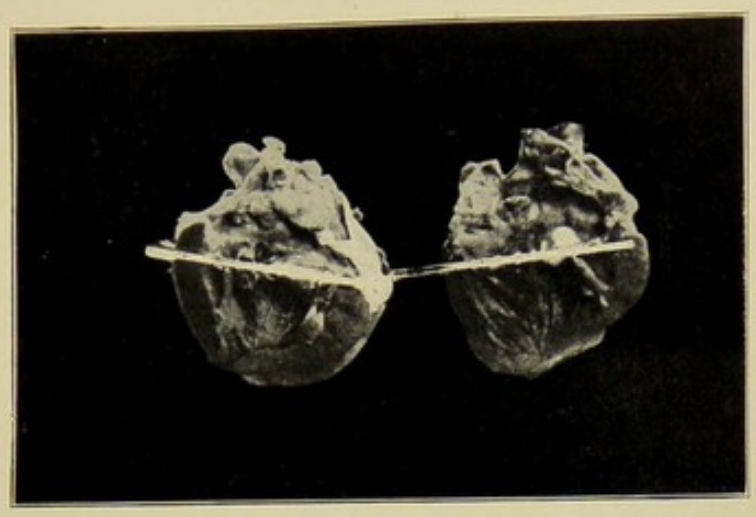


FIG. 58

Experimental rheumatic endocarditis ("simple") in a rabbit, produced by intravenous inoculation of the diplococcus. The heart on the left side is normal. On the right side minute vegetations are seen immediately in front of the glass rod; their minute size and the absence of colour-contrast makes their reproduction by ordinary photography exceedingly difficult.

FIG. 59

Heart of a rabbit. Left auricle and ventricle opened, showing extensive malignant endocarditis of the mitral valve. The lesion was the result of intravenous inoculation with the *Diplococcus rheumaticus*.

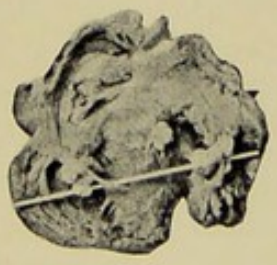


FIG. 60

The heart of a rabbit. The left auricle and ventricle are opened and a glass rod passed under two small vegetations intermediate in size between those occurring in "simple" and "malignant" endocarditis.

and two specimens of simple endocarditis caused by it are shown among the macroscopic specimens.

For some months the organism had been kept growing in the acid milk medium, but it had not of late been passed through an animal, and we were doubtful whether it had not completely lost all virulence.

The organism was transferred to blood agar tubes in the usual manner, and an exceptionally large amount used for inoculation.

The temperature upon the next day was 103° F., but until the fourteenth day we noticed no change at all, and then we found the heart very excited. This in a rabbit is not a reliable sign of cardiac disease, and as there was no murmur we somewhat hastily concluded that there was no result to be expected. The animal was found dead on the nineteenth day.

The necropsy made the cause of death quite clear. The heart was large and the cavity of the left ventricle dilated. Vegetative endocarditis of the aortic valve had practically closed the lumen of the aorta, and the aortic ring was thickened. Minute beads were found fringing the mitral valve, and its aortic cusp was thickened by previous endocarditis.

From the aortic vegetations the diplococcus was isolated, and was demonstrated in the sections of the valve. There were no infarcts. It must, we think, be allowed that this was a very remarkable and suggestive result.

Two macroscopic specimens of rabbits' hearts are also shown, one resulting from an injection with the *Diplococcus rheumaticus*, and one from the diplococcus obtained from a case of malignant endocarditis, which illustrate the transitional phases of the endocarditis, and also a third specimen showing primary malignant tricuspid endocarditis produced by the diplococcus of rheumatic fever.

The remainder of the series of experimental investigations we must record very briefly. These investigations were made with the *Streptococcus pyogenes*, and emphasise, we believe, the salient points of our previous results.

Upon two occasions virulent cultures of the *Streptococcus pyogenes* obtained from a case of puerperal fever were supplied to us from the Jenner Institute. The virulence had been increased by passing the organism through a series of rabbits,

and the cultures that we received may be looked upon as characteristic of the virulent *Streptococcus pyogenes.*

We treated this micro-organism in the same way that we have the *Diplococcus rheumaticus,* that is, transferred it first to the acid medium, and thence to blood agar. The only difference in detail was the use for inoculation of a small part of the growth from one tube instead of the growth from some four or six tubes. With such a small quantity as this, in our experience, no result is obtained with the diplococcus of rheumatic fever.

The rabbits died in every instance within twenty-four hours of inoculation. The post-mortem appearances differed widely from those which we have previously described. There were hæmorrhages from the mucous surfaces. The blood was fluid, the spleen large, dark and soft, the kidneys pale and extremely friable. There were no local lesions, such as arthritis or endocarditis. Microscopic examination of the organs showed great numbers of streptococci in the blood capillaries and tissues.

On each occasion this condition of septicæmia resulted, and although we cultivated the streptococcus for a week in the acid medium (a medium which is not considered to be a favourable one), the result on inoculation was the same.

It may be objected to these results that the virulence of the streptococcus had been artificially raised, and that they are not therefore comparable to our previous investigations, but this objection cannot be raised against the next case. A woman was admitted to St. Mary's Hospital, suffering from septic absorption from a suppurative phlebitis. An operation cured her, and from the pus the *Streptococcus pyogenes* was isolated and cultivated in the acid medium, and then transferred to blood agar. Intravenous inoculation of a rabbit resulted in death within twenty-four hours from a condition of septicæmia of the same nature as that which resulted from the streptococcus sent to us from the Jenner Institute.

The last experiment was made with a streptococcus isolated from the pus of a suppurative pericarditis. The patient, a boy, had died from a streptococcus pyæmia, the result of a punctured wound of the right knee-joint.

The same procedure was adopted as before, and on this

FIG. 61

Section through the necrotic tissue of a vegetation on the mitral valve (rabbit). Experimental malignant rheumatic endocarditis. Vast numbers of diplococci are visible. *Cf.* Fig. 55. (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

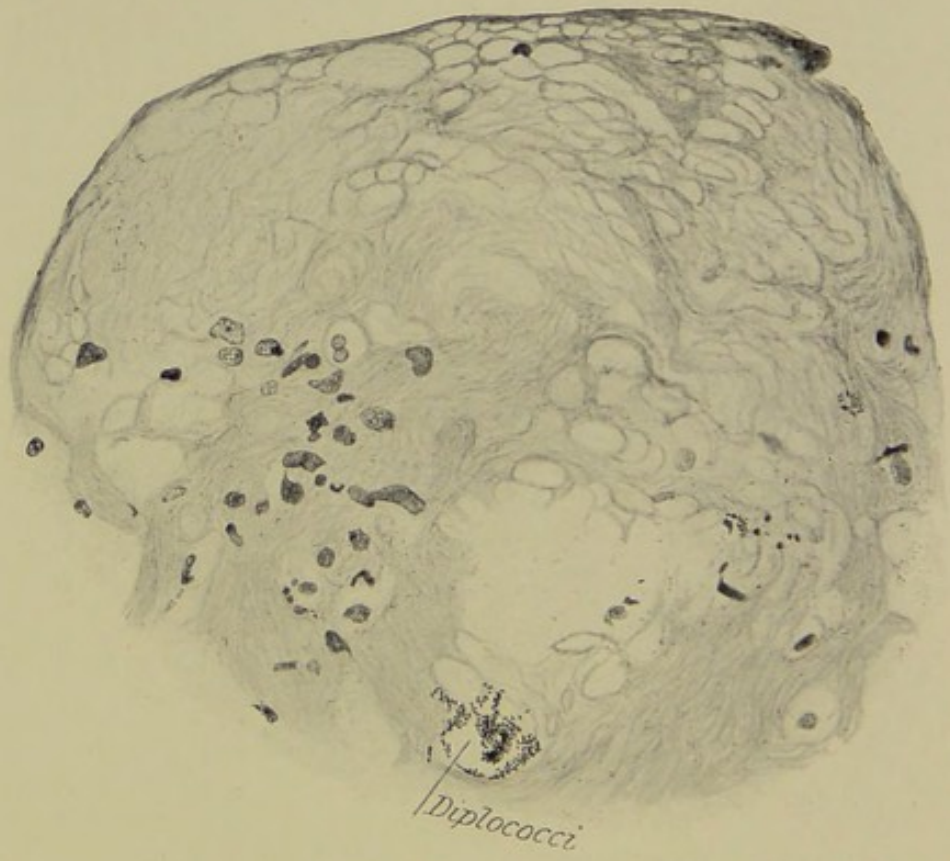


FIG. 62

Section of the mitral valve of a rabbit. Experimental "simple" endocarditis showing diplococci. (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

occasion the rabbit lived for five days, during which time arthritis of the right carpal joint developed.

The post-mortem showed purulent arthritis, small abscesses in the liver and both lungs, a clear exudation in the pericardium, and a fibrino-cellular exudation in the pleuræ. There was no endocarditis.

These investigations with the *Streptococcus pyogenes* serve to show more distinctly the definite character of the results we have obtained with the diplococcus of rheumatic fever and the diplococcus isolated from certain cases of malignant endocarditis. We do not pretend for a moment that they settle the question of the relation of these various processes to one another, but they demonstrate that, as in man, characteristic rheumatic fever and this type of malignant endocarditis on the one hand and pyæmia and septicæmia from the *Streptococcus pyogenes* on the other are different conditions, and suggest that there must be some very definite reason for such differences.

These clinical cases, the experimental investigations, and our specimens show, we believe :

Firstly, that the probability that some of these cases of malignant endocarditis are rheumatic is not contrary to clinical experience.

Secondly, that a diplococcus is the cause of some of these cases of malignant endocarditis.

Thirdly, that this diplococcus will reproduce in rabbits malignant endocarditis, and also a condition we consider to be rheumatic fever.

Fourthly, that the *Diplococcus rheumaticus* will produce malignant endocarditis.

(B) *Histology*

The minute anatomy of the two conditions is the next consideration.

If a necropsy is made upon a characteristic case of rheumatic fever and upon a case of malignant endocarditis of the type under consideration, the most striking feature in which they differ is found to be the condition of the damaged cardiac valves.

In acute rheumatism there are minute vegetations, in malignant endocarditis there are, as a rule, large exuberant masses, with possibly also ulceration of the valve substance

and rupture of chordæ tendineæ. Yet these large vegetations, save in one respect, do not differ in their microscopic structure from the minute ones. There is the same necrosis, the same cell infiltration, the same swelling of the connective tissue.

If a careful search is made in the damaged valve of rheumatic fever, the diplococci may be found in regions where the process has not reached the limit of necrosis though the search is not easy because the fibrous framework of the valve is not an easy structure to examine minutely. If search is made in the necrotic part of the vegetation, all attempt to demonstrate the micro-organisms may and probably will be met with failure ; they have been for the most part destroyed. But in malignant endocarditis they are found in masses, sometimes fringing the free edge of the vegetation, sometimes buried in the necrotic tissue.

This then, we believe, is the essential difference in the morbid anatomy of the two conditions. Hence it is that in rheumatic fever, death does not occur from acute endocarditis but from peri- and myo-carditis, whilst in malignant endocarditis death occurs almost invariably from endocarditis and its secondary results ; though occasionally during the illness, sometimes within the last few days of life, pericarditis may develop. Hence it is that numerous white infarcts occur in the malignant form, and are exceptional in the simple. The white infarcts need no detached clot or fragment of vegetation for their formation, it is sufficient that a considerable mass of the micro-organisms be carried to the spot, and there set up by their poisonous action the phenomenon of coagulation necrosis. Upon innumerable occasions these organisms, which grow so vigorously in the vegetation, are scattered in every direction by the blood stream, and give rise to the irregular fever, the sweating, the prostration, and wasting. In the heart the process steadily advances, but it by no means follows, and indeed does not follow, that the secondary foci in the various viscera will also of necessity steadily progress. The place of election in this disease is the heart, and no one can seriously doubt that the chemistry of each particular organ of the body must be in some measure peculiar, and it is not strange that while the process is spreading in the heart an infarct in the kidney, for example, may be healing.

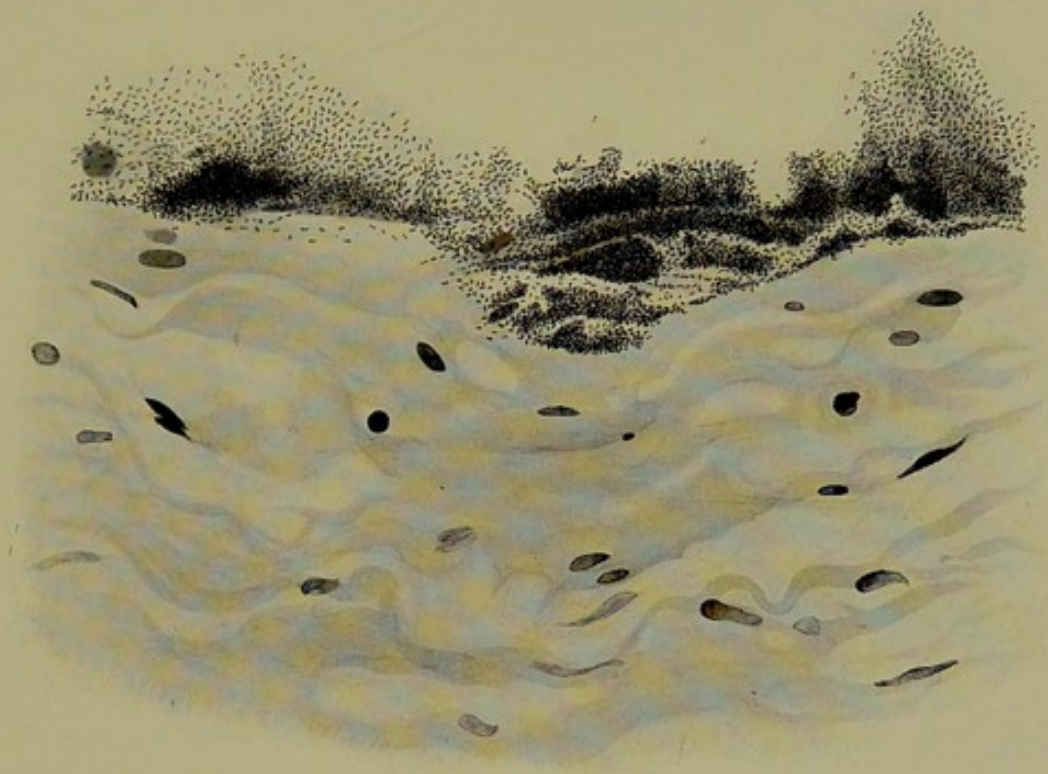


FIG. 63

Section through the mitral valve (human), from a case of rheumatic fever and chorea. Numerous diplococci were present in the tissues. Masses of diplococci were also present in the cerebral cortex (*vide* Fig. 64) (Zeiss, obj. $\frac{1}{12}$, oc. 3). The vegetations were minute.

The clinical distinction between a characteristic rheumatic fever and malignant endocarditis is wide, and the difference in the vegetations in the two conditions is equally wide, but just as the two clinical conditions merge the one into the other, so, too, do these vegetations. In some cases of rheumatic fever there may be many diplococci in the valves. In some cases of malignant endocarditis the vast majority of the micro-organisms are destroyed. The first represent cases of rheumatic fever, which toward the end approach the type of malignant endocarditis; the second represent those cases of subacute malignant endocarditis of long duration in which the virulence appears to be low in intensity, but persistent in character.

There does not appear to us to be any essential difference in the morbid anatomy of the two conditions other than this, that for some occult reason the micro-organism in the malignant type, instead of being destroyed in the vegetation, survives and multiplies. It also seems unlikely to us that the organisms *select* a previously damaged valve—the results of experiment indeed, decided against this; it is more probable that there is in this type, as in rheumatic fever, that same tendency for the diplococci to attack the cardiac valves, and that damaged valves from lack of full power of resistance permit the rapid and continual growth of the micro-organisms, and in this way predispose to the malignant type of the disease.

(c) *Bacteriological Details*

To turn now to some of the bacteriological details. We have no knowledge of the occurrence of the diplococcus we have isolated from these cases of malignant endocarditis outside the body, except in so far as we have studied it in culture. In the body it is present in the local lesions which characterise the disease, and in these situations it may be discovered by staining sections of those morbid structures with appropriate dyes, though more readily still by treating films made from scrapings of these tissues.

The organism is stained best by the aniline dyes, but in our experience, though it stains by Gram's method, it does not retain the stain with tenacity. It may be present in the vegetations upon the cardiac valves in enormous numbers

where it can be seen in the substance of the vegetation, and also in large masses in direct contact with the blood stream.

In this situation it is present as a minute diplococcus, measuring 0.5μ or even less in diameter. We have isolated it in pure culture by the incubation of scrapings of the vegetation in a mixture of bouillon and milk slightly acidified with lactic acid, a medium such as we used for isolating the diplococcus from cases of rheumatic fever. When cultivated in this manner it resembled very closely the latter organism, though it is slightly smaller, and may grow in longer chains in fluid media, and form more definite masses upon the solid ones. Such differences as these, we believe, can be explained by its more rapid growth.

In sub-cultures made upon blood agar, which is very suitable for maintaining its virulence, the difference between these two organisms is hardly discernible. Both form upon this medium discrete colonies of minute size, the smaller and younger of which are translucent, the older and larger opaque, and of a yellowish colour. On ordinary media the growths of the two organisms are strikingly similar. Thus in bouillon they form a slightly granular deposit on the sides and bottom of the tube, while the supernatant fluid remains clear. On gelatine both form discrete non-liquefying colonies, but these media are not suitable for its growth.

Both these organisms coagulate the milk medium, forming a firm coagulum, but the diplococcus from the malignant type the more rapidly. By both, alkaline media are rendered very distinctly acid.

This acid-producing property is a well-known feature in the growth of many bacteria. Dr. Sidney Martin, in his important researches upon the poisons of infective endocarditis, attributed this to a non-proteid body. When we recall how much attention has been directed to the possibility of some acid-producing process in the metabolism of rheumatic affections, and when we bear in mind the wide-spread belief in the value of treatment by alkalis, we are led to wonder whether sufficient attention has been given by clinicians to this result of bacterial growth in rheumatic and gouty affections. Is it not possible that in a gouty subject an attack of gout may result from an infection with these acid-producing bacteria ?

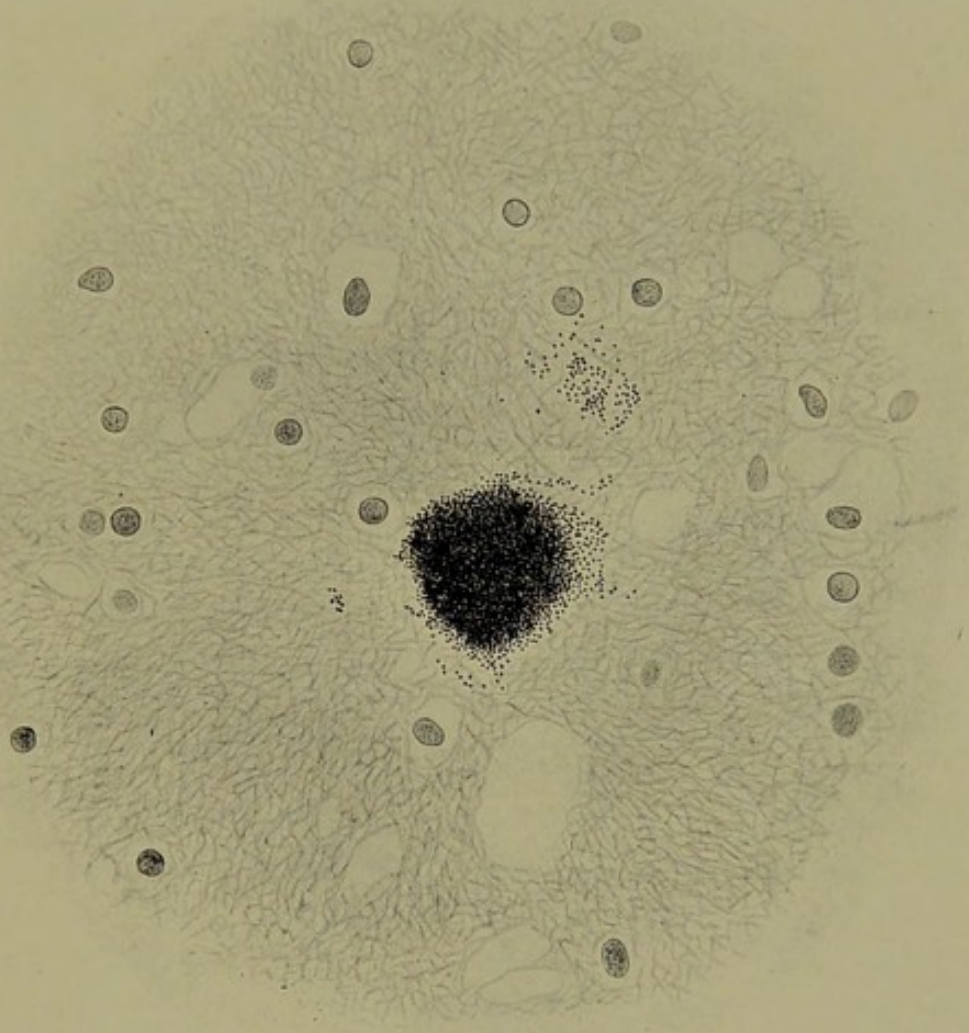


FIG. 64

Human chorea. Section through the motor cortex showing a mass of diplococci in the neuroglia: the diplococci were also demonstrated in the mitral valve. (Zeiss, obj. $\frac{1}{12}$, oc. 3.)

The pathological action of the organism was studied by isolating it in the milk and bouillon medium and then transferring it to blood agar. Injections were made directly into the circulation of rabbits through the auricular vein.

III. Concluding Observations

(A) *Upon the Specific Nature of Rheumatic Fever*

Finally, it remains for us to touch very briefly upon some of the considerations that arise if it be true that some cases of malignant endocarditis are rheumatic in origin. In these considerations, much must turn upon the question whether rheumatic fever is a specific disease. If it be a specific disease the processes involved must be specific, and the problem arises to what extent this specific character is due to the poisons which are formed by the micro-organism, and to what extent to the peculiar tissue reactions. As knowledge upon this problem is gained, the mode of origin of the malignant type may become apparent. Again, whatever the nature of the poisons that are formed in rheumatic fever, those of this type of malignant endocarditis would be allied to them, a conclusion which, in the future, may have a close bearing upon the treatment of the disease.

(B) *Upon the Relation of Septic to Rheumatic Processes*

An interesting point which arises from this question of the specific nature of rheumatic fever is the relation of rheumatic to septic processes. Are these distinct in their essence, or is rheumatic fever an infection with attenuated pyogenic micrococci, as Singer [3] maintains ?

We have been compelled to differ from Singer because we have isolated only one organism from rheumatic fever ; nevertheless, this question must still arise in a slightly modified form thus : Is this diplococcus we have isolated the attenuated *Streptococcus pyogenes*, and rheumatism a result of this attenuation ? In reply to this we would ask, can the term " attenuation " be applied in this sense ?

Chemical pathology will, we suppose, solve this question, and meantime we are driven back to clinical experience, and ask of it once more, is rheumatic fever a specific disease ? If it is, the diplococcus, call it what you will, must be to this extent specific, that it has produced a constant disease. It

is to be hoped that this problem of the relation of rheumatic to septic processes will be solved before very long, and if the diplococcus described by ourselves and others proves to be the only cause of rheumatic fever, this solution will mark another step in the progress of our knowledge.

(c) *The Position that this Type of Malignant Endocarditis occupies*

Again, if the two processes, rheumatic and septic, are essentially different, then, we suppose, mild acute rheumatism corresponds to the milder forms of pyæmia, virulent rheumatism to severe pyæmia; this form of endocarditis to malignant endocarditis with suppuration, while septicæmia perhaps finds a parallel in some cases of rheumatism with profound toxæmia.

We have undertaken some investigations into this subject—starting from the assumption that the micro-organisms isolated from *distinct types* of rheumatic and septic diseases should, if placed under the same conditions out of the body, produce also distinct types of disease in susceptible animals.

Thus from rheumatic fever, puerperal fever, suppurative phlebitis, pyæmia, and cellulitis, we have isolated the organisms, and have endeavoured, as far as possible, to maintain their virulence by transferring them at once to blood agar. Rabbits have been injected with these cultures, but as yet pyæmia has not resulted from the *Diplococcus rheumaticus*, or rheumatic fever from the pyogenic organisms. Triboulet records the same experience.[4] We do not pretend these investigations are by any means sufficient to settle this question; but we make allusion to them because it does seem an important point in the study of the large group of pathogenic micrococci to choose typical examples of the disease of which they are thought to be the cause, and then to put these organisms to the test of experiment under similar conditions, rather than to deal with cultures, the virulence of which has been artificially raised, or with organisms that have been placed upon various media far removed from their natural soil.

(d) *Local Malignancy in other Rheumatic Manifestations*

To the assertion that these cases of malignant endocarditis are rheumatic the fair criticism may be raised that such

persistent local processes should be met with also in other of the rheumatic manifestations. It cannot be supposed that any lesion, except of the heart or great blood-vessels, would produce the same condition of blood infection as does the malignant endocarditis, for there will not be that same relation of the local lesions to the general blood stream.

1. *Malignant pericarditis.* Yet it is well recognised that there is in childhood a persistent intractable malignant form of pericarditis. This may smoulder on for months, the process throughout being a repeated local pericarditis, never an acute general inflammation. In such a condition as this, if the organisms in the pericardium had the same easy access to the general circulation that they have in the vegetation of a valve, we should suspect the similar character of the two conditions would be at once apparent.

2. *Malignant arthritis and rheumatoid arthritis.* It is probable, too, that the same process occurs sometimes in the joints, and gives rise to chronic destructive lesions of one or more, a condition included in the disease of joints known as rheumatoid arthritis. Such a condition of the joints need not react to treatment by salicylate of soda any more than do the conditions of endocarditis or pericarditis.

(E) *The Insidious Onset of Rheumatic Fever.*

Another criticism of the investigation that may be raised from the clinical side is, that though malignant endocarditis and rheumatic fever may in their course sometimes resemble one another, their modes of onset are widely different. The onset of rheumatic fever, it may be said, is comparatively acute ; of this type of malignant endocarditis almost invariably very gradual.

Rheumatic fever, no doubt, does very often commence somewhat acutely, but in childhood we are repeatedly met with the history that before the definite rheumatic symptoms were noticed the child had been out of health, was becoming anæmic and irritable, and was losing flesh. If the temperature is taken it may be found to be raised during this period. The onset of rheumatic fever is then often insidious, as Sir William Church emphasised in his article upon acute rheumatism in Professor Clifford Allbutt's "System of Medicine." It appears to us that observations in every direction tend to

strengthen the view that this diplococcus may live for long periods in the body, as it certainly does in culture outside the body. Possibly it may remain latent; often it produces indeterminate symptoms, and finally it may produce characteristic symptoms. The repeated relapses of the chronic types of rheumatic fever are most probably to be explained in this resistance of the micro-organism to complete destruction.

We must once more thank Dr. W. B. Cheadle and Dr. D. B. Lees for leave to make use of their clinical cases. It would be impossible, if it were not for this assistance, to collect sufficient data for the generalisations which are essential in investigations of this nature. To Mr. H. G. Plimmer, Pathologist to St. Mary's Hospital, we must also again express our indebtedness.

REFERENCES

[1] "Ueber die maligne (Nichtseptische) Form der Endocarditis Rheumatica," *Berliner klinische Wochenschrift*, 1899, No. 29, p. 644.

[2] "Ueber den Infectiosen-Charakter und den Zusammenhang von acuten Gelenkrheumatismus und Chorea," *Berliner klinische Wochenschrift*, 1899, No. 29, p. 638.

[3] "Weitere Erfahrungen uber die Aetiologie des acuten Gelenkrheumatismus," *Wiener klinischen Wochenschrift*, Jahrgang 1901, No. 20.

[4] "Le Rhumatisme Articulaire Aigu," 1901.

PAPER NO. XVI

A CONTRIBUTION TO THE STUDY OF RHEUMATIC IRITIS

(Reprinted from vol. xxiii of the *Ophthalmological Society's Transactions*)

This paper gives a short account of the experimental production of iritis by intravenous inoculation of the diplococcus, and considers the bearing of the results upon the occurrence of rheumatic iritis in man.

Introductory

Before we commence this paper we must define our position. We do not pretend to that skilled knowledge of irido-cyclitis which would be asked of an expert, but have —when investigating the subject of rheumatic fever—observed certain facts which may be of interest to ophthalmic surgeons, and which in this spirit we bring before you on this occasion.

For us rheumatic iritis is rather an incident in a general infection than in itself a disease, and for our purpose it matters little whether it is rare or frequent in its occurrence. The question, as it presents itself, is sufficiently simple : Can a micro-organism which is a cause of rheumatic fever produce iritis as it does endocarditis, pericarditis, arthritis, pleuritis, and subcutaneous nodules ?

For the ophthalmic surgeon the subject is much more complex, involving points in treatment and refinements in diagnosis and management to which we need not now allude. For him it is a disease of first importance ; for us it is, as we have said, an incident in a general infection.

The Clinical Position of Acute Rheumatic Iritis

Among ophthalmic surgeons we believe there is some divergence of opinion as to the frequency and occurrence

of acute rheumatic iritis, though there appears to be little doubt that it is a rare, but not unknown event—a statement which we would venture to support with such experience as we have had ourselves. Further support of its rarity was supplied in January 1903, by Macrae, in the *Journal of the American Medical Association*, who noted its occurrence only once in 270 cases of rheumatic fever.

A good example of the condition was published in the *British Medical Journal* for March 7, 1903, by Mr. F. C. Forster, of Lowestoft, and in addition Mr. Forster kindly sent us in a letter some further details, which we have his leave to quote. It may perhaps be remembered that it was the case of a girl, 12½ years of age, who developed, after a definite chill, tonsillitis and arthritis. Then followed chorea, and later iritis of the right eye and endocarditis. In his letter Mr. Forster writes as follows: "The iritis came on very suddenly when she was recovering from chorea. The right eye alone was affected; the pupil was altered in shape, and a naturally brown eye assumed a yellow tinge. . . . There was the usual marked congestion (especially circumcorneal), with great pain and photophobia; the pain was both topical and supra-orbital. . . . The iritis relapsed twice, and I feared that some posterior synechiæ would eventually lead to diminution of vision. . . . Recovery was eventually good. Rheumatic iritis," he adds, "is, of course, not common in children, but I have met with few more typical than the one under discussion. Syphilis, gonorrhœa, and trauma may certainly be excluded as causes in this particular case."

This seems to us a clear example of acute rheumatic iritis of unusual severity. Such examples as we have seen have been very transient.

Among those who are opposed to the acceptance of acute rheumatic iritis, much importance is attached to the gonorrhœal infection. Even if this may have occurred some years before, they attribute an iritis of a rheumatic type to that cause. In passing we would venture to point out the well-known fact that rheumatic symptoms are most liable to occur in those subjects of gonorrhœa who have suffered previously from rheumatic fever; also that the diplococcus of the gonorrhœal affection was one of the earliest known of this type of micro-organism, and its recognition established

in text-books on hard and fast lines, which with more mature experience are perhaps a little too hard and fast ; and, lastly, that the rheumatic infection equally as much as the gonorrhœal is liable to lurk in the system for long periods. Both diseases may theoretically be causes of iritis. Both linger in the system. We are thus in agreement with Mr. Lawford's opinion as expressed at the British Medical Association meeting in August 1901, on the imperfection of this *proof* of the gonorrhœal origin of many cases of iritis.

The Object of the Communication

The object of our communication is to show that acute iritis may result in rabbits from experimental inoculations with a diplococcus or micrococcus which is a cause of rheumatic fever.

Other observers—for example, Birch-Hirschfeld—have produced septic panophthalmitis by inoculations from cases of septic endocarditis, but in our two cases the micro-organism was isolated, first, from a case of ordinary rheumatic fever in a child, and, secondly, from a case of malignant endocarditis of rheumatic origin, and in neither animal did there result septic panophthalmitis.

The cases we will detail immediately, but we first emphasise the fact that these inoculations were intravenous—into the auricular veins of rabbits,—and not local—into the eye. Had they resulted from local inoculations we should not personally have attached any importance to them.

The Investigation

Case 1. In 1899 a boy of 9 years, who was suffering from morbus cordis, developed, while under observation, active rheumatism—that is to say, arthritis, pericarditis, and subcutaneous nodules. Death resulted from pericarditis. From the pericardial fluid, which was clear but contained also flakes of exudation, minute diplococci were isolated. They were also demonstrated in films of the pericardial fluid, in which they grew in chains. The necropsy showed the usual results of rheumatic fever in childhood—there was no suppuration.

The first rabbit inoculated intravenously with the pericardial fluid died on the ninth day of arthritis, pericarditis,

and broncho-pneumonia. The second died on the twentieth day with arthritis and pericarditis. The third recovered. The fourth was killed on the tenth day, and suffered from arthritis and mitral endocarditis. The fifth was killed on the ninth day, and suffered from pericarditis, pleurisy, endocarditis, pneumonia, and arthritis. The sixth developed choreiform movements, and was killed. The seventh died of malignant endocarditis. The eighth died, on the tenth day, of pericarditis and endocarditis with an infarct in the left lung. It was this animal that developed iritis of the left eye. The ninth developed chronic rheumatic arthritis; and then we lost the strain, failing to recover the organisms from the exudation. Thus it will be seen that of a series of nine animals only one developed iritis. There was nothing unusual about the inoculation, but the animal was a feeble one. On the fifth day there was some lacrymation; this continued for two days and then followed injection of the conjunctival vessels, discoloration of the iris, and considerable exudation into the anterior chamber. It should be clearly stated that the appearance was not like that of an hypopyon, and after death the fluid was not opaque and yellow, but a little cloudy, although, as will be seen, it contained vast numbers of the micro-organism. The condition in no way resembled one of septic panophthalmitis. It was an easy matter to grow the micro-organism again from the fluid in the anterior chamber, and it showed the usual characters. The next rabbit inoculated developed chronic arthritis.

Under the three microscopes there are shown:

(1) A film of the exudation.

(2) A section of the iris under a low power showing the exudation, fibrino-cellular in character, on the anterior surface of the iris.

(3) The same under a high power showing the micrococci in the exudation.

The anterior surface of the iris, after removal, was seen to be dotted over with small, raised, white areas.

The minute description of the changes is given with the drawings placed beside the microscopes.

Since that investigation we have repeatedly studied the illness produced in rabbits by the injection of this micrococcus, and although we have from time to time noticed

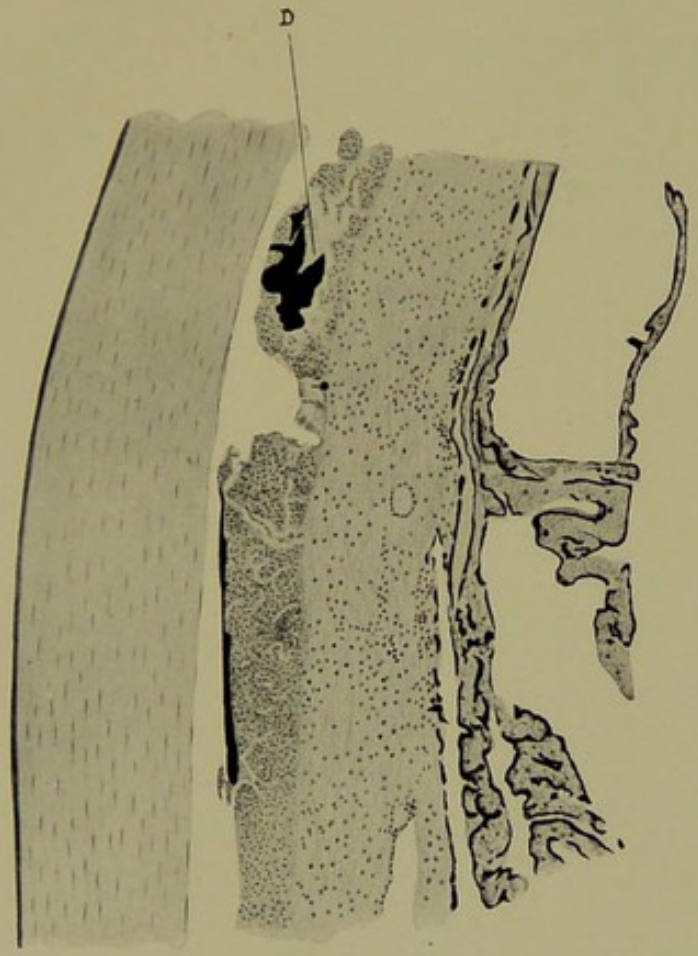


FIG. 65

Experimental rheumatic iritis produced in a rabbit by intravenous inoculation of the diplococcus. (Low power.) D. Diplococci.

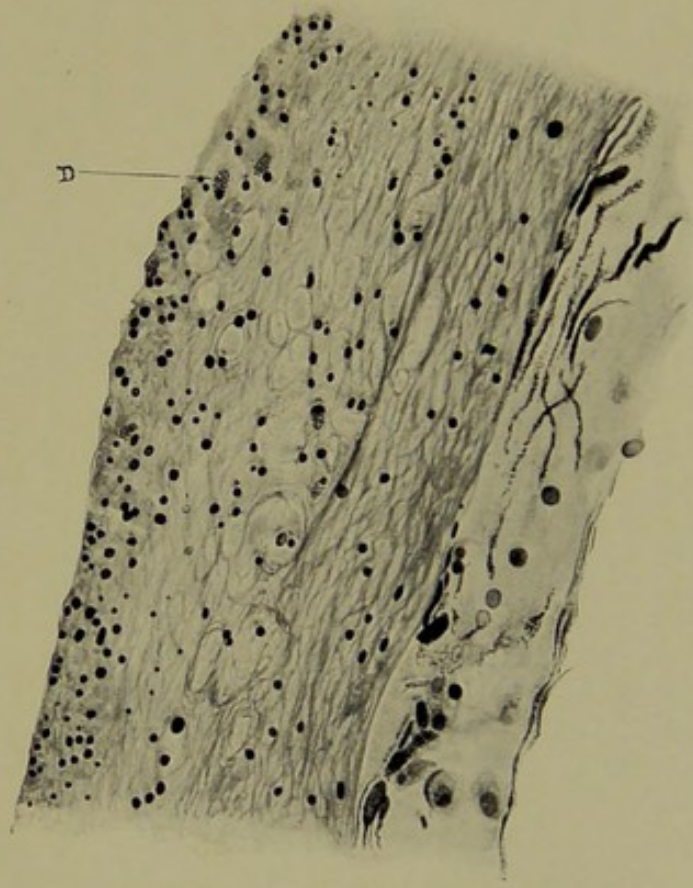


FIG. 66

Portion of the same more highly magnified, showing the inflamed iris. D. Diplococci.

lacrymation and slight conjunctivitis, we have only once met with iritis again, and that with a culture obtained from the malignant type of rheumatic endocarditis.

CASE 2. A boy aged 13 years, in December 1900, was admitted under Dr. Lees to St. Mary's Hospital for heart disease. He had suffered two years before from an attack of rheumatic fever. The present illness had commenced insidiously. Mitral and aortic disease were discovered; the boy went from bad to worse, and died rather unexpectedly in January 1901.

General pericardial adhesion, malignant mitral and aortic endocarditis, and a splenic infarction were found. There was no suppuration. Two hours after death we isolated from the cardiac valves a minute diplococcus.

Intravenous inoculations were made.

Rabbit No. 1 died of malignant mitral endocarditis with iritis.
" " 2 " pericarditis and endocarditis.
" " 3 " pericarditis and endocarditis.
" " 4 " pericarditis.
" " 5 recovered.

It is remarkable and interesting that in a considerable number of investigations we have only met with iritis twice; and that Fritz Meyer, who has made extensive experiments with animals with a smilar organism, does not mention its occurrence. Nor, to our knowledge, have Dr. Ainley Walker and Dr. Beaton met with it. It must, we think, be a rare occurrence, as in man.

There is still a great gap in our knowledge. For no one, so far as we are aware, has isolated this organism from a case of rheumatic iritis in man and produced rheumatic fever in animals. We have waited in vain for such an opportunity for three years, and bring this forward in the hope that some one may complete the chain of evidence.

PAPER NO. XVII

ON THE RELATION OF THE STAPHYLOCOCCUS PYOGENES AUREUS TO RHEUMATIC FEVER

By Dr. F. J. POYNTON and Dr. W. V. SHAW.

(Reprinted from the *Transactions of the Pathological Society of London*, 1904)

Dr. Vernon Shaw, who had previously demonstrated the experimental production of acute rheumatism in monkeys, collaborated in this paper, which deals primarily with a statement that has been made to the effect that acute rheumatism is an attenuated pyæmia. A frankly pyæmic type of infection is chosen in the staphylococcal pyogenes aureus, and this micrococcus and the results it produces in man, monkeys, and rabbits compared with those produced by the diplococcus of acute rheumatism. An attempt is made in the second part of this paper to investigate multiple infections, a line of investigation which in the future promises to throw fresh light upon the problem of rheumatism and its relation to other micrococcal infections.

The object of this paper is to continue the series of investigations which have been made in recent years upon the infective origin of rheumatic fever, and to uphold the view that the disease, is, in all probability, a special one, for the clinical entity has already been established by the careful investigations of experienced observers. We rely for our evidence upon clinical, pathological, and experimental studies, firmly believing that it is only by a broad survey of the question that the problems of rheumatic fever can be solved. It is, we believe, essential to place the bacteriological and experimental results side by side with the clinical course of the disease in man, in order to avoid the danger of becoming involved in side issues or half-truths, and in support of this we would instance one example, that of endocarditis. All must admit that this is an

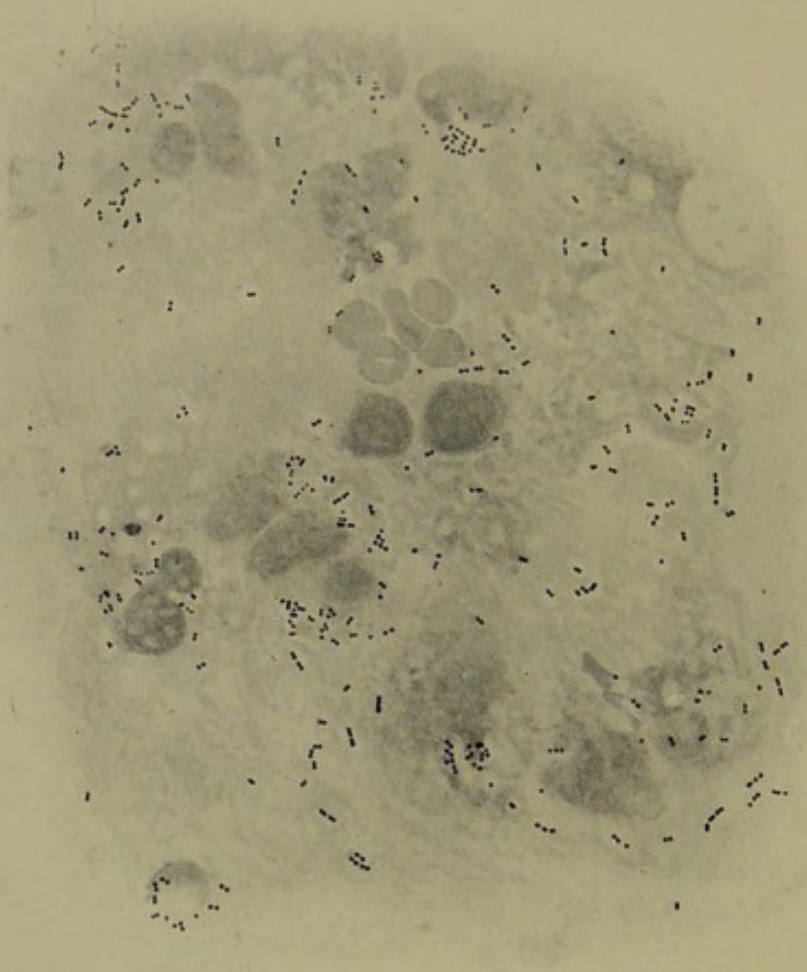


FIG. 67

Experimental rheumatic arthritis. Film from exudation in the knee-joint of a monkey intravenously injected with the diplococcus. (Zeiss, $\frac{1}{12}$, oc. 4.) The animal had recovered from a previous mild attack of arthritis, but succumbed to a second culture, taken two hours after death, from a child dead of rheumatic fever : death occurred on the fifth day from mitral and aortic endocarditis with myocarditis.

important result of rheumatic fever, and a direct consequence of the disease, for there is no trustworthy evidence to point to it as an indirect or secondary result. All must admit, too, that the allied infections, the pneumococcal, the stapylococcal, gonococcal, and streptococcal (pyogenes so called), may also in some instances produce endocarditis, but the series of events, and the course and history of the cases in any of these infections, are different from the accepted course of a true rheumatism. Again, until recently, experimental endocarditis was a rare occurrence, but now it is a frequent one, for this reason, that a diplococcus obtained from the damaged valves in that very disease, rheumatic fever, which above all causes endocarditis, possesses the power of producing experimental endocarditis, with remarkable constancy. Yet in spite of this there are some investigators who draw the conclusion that experiment in this matter is useless, because they have found, naturally enough, that the other micrococci will also sometimes produce endocarditis in animals as they will in man. With that conclusion we do not agree. Another inference that has been drawn is that because some of these other micrococci have produced endocarditis, they are also capable of producing rheumatic fever. We believe that also is a dangerous inference, and not warranted by a true and careful consideration of the facts. Neither do we believe that rheumatic fever can be considered an example of an attenuated pyæmia in a commonly accepted meaning of the term pyæmia.

At this point we wish to put before you very definitely our view on this question of rheumatic fever considered as an attenuated pyæmia. If those who hold this view imply by it that rheumatic fever is a disease of the pyæmic type in that it shows various local lesions, which contain within themselves at one time or another the infective agent, and further if they wish to emphasise that these lesions tend to take as a rule a benign course, then we also are quite in accord with that view which has been taught us by earlier investigators. But if they wish to imply, as many do, that any disease of the pyæmic type, that is any disease which causes multiple abscesses, will, when of a mild type, produce rheumatic fever, we are opposed to them. They then clearly hold that the disease is not an entity, while we hold that it is as definite an

entity as tuberculosis. If the view be accepted that rheumatic fever is not an entity but is an attenuated pyæmia, it should follow that the *Staphylococcus aureus*, itself a most important cause of pyæmia in man, should also be in its attenuated state a frequent cause of rheumatic fever. But we shall attempt to show that in our experience far from the *Staphylococcus aureus* being a frequent cause of rheumatic fever, it is not a cause of this disease at all, and that therefore the vague conception of rheumatic fever as an attenuated pyæmia must be abandoned so far as the *Staphylococcus aureus* is concerned.

We take as our type of rheumatic fever the disease as it occurs in childhood and in the young adult, and rely entirely on fatal cases which post-mortem examinations have confirmed as the true disease. In this way alone can we hope to start from some point of agreement, for we believe that no one will dispute that the post-mortem evidences of rheumatic fever are very definite ones, and on the other hand, that if there is not a post-mortem examination it is always open to any objector to question the diagnosis.

It is first essential for us to show that it is possible with reasonable care to distinguish the two micro-organisms, the *Staphylococcus aureus* and *Diplococcus rheumaticus*, as the following data will show.

A. The *Staphylococcus pyogenes aureus* is about 1.0μ in diameter, and grows in irregular clumps. It is usually a micrococcus.

The *Diplococcus rheumaticus* measures about 0.5μ in diameter, and grows in masses on solid media and in chains in liquid media. It is usually a diplococcus.

B. The staphylococcus stains well by Gram's method.

The diplococcus stains feebly by Gram's method.

C. The staphylococcus liquefies gelatine.

The diplococcus does not liquefy gelatine.

D. The staphylococcus grows freely on agar, forming a smooth, white, shining, opaque layer, which on exposure becomes of a deep yellow colour.

The diplococcus grows (but not freely) on agar, forming minute, discrete, white, slightly opaque colonies, and there is no development of colour.

The same is true of litmus agar.

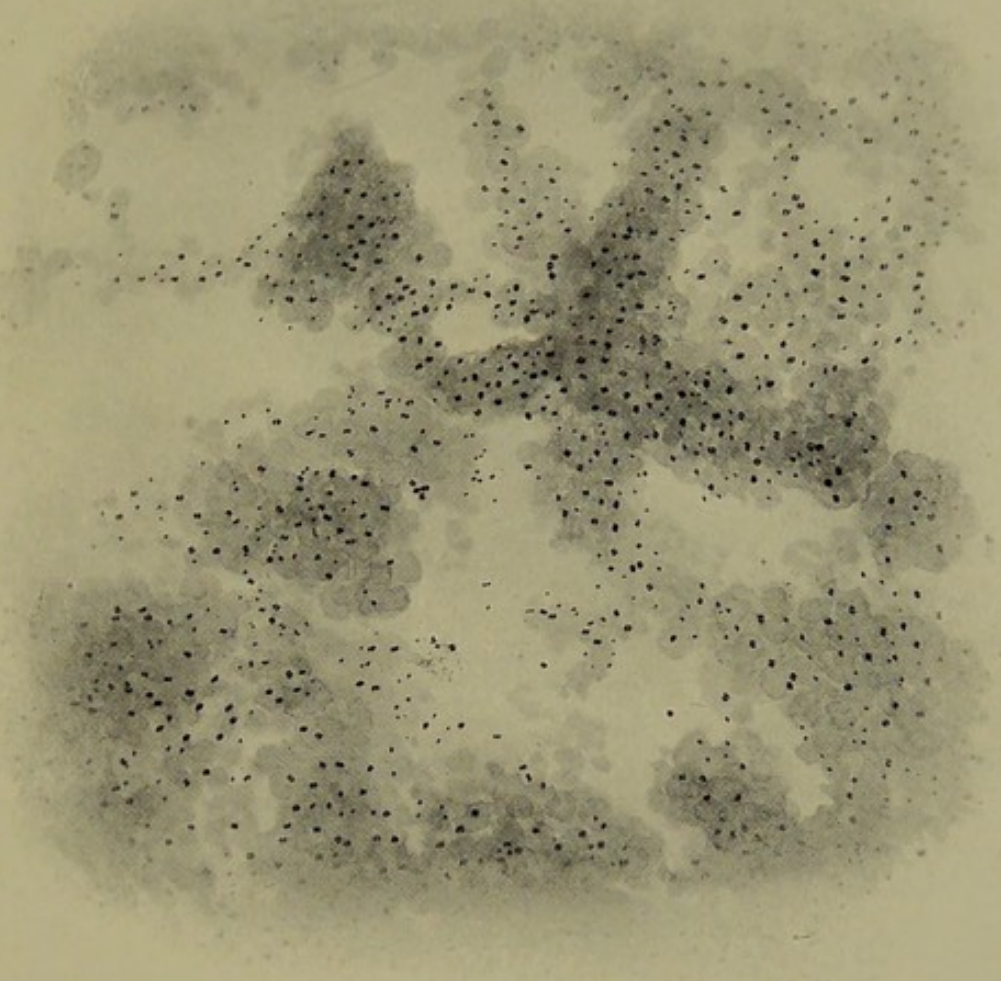


FIG. 68

Experimental arthritis. A film from the exudation in the knee-joint of a rabbit dead from the intravenous injection of the *Staphylococcus aureus*. The animal died of pyæmia on the third day. (Zeiss, obj. $\frac{1}{12}$, oc. 4.)

E. The staphylococcus growing in bouillon makes the fluid at first turbid, and later clear with a yellowish sediment.

The diplococcus in the same medium forms a flocculent white precipitate leaving the supernatant fluid clear.

F. The staphylococcus upon potato gives an abundant yellow growth.

The diplococcus grows feebly upon the same medium, forming minute discrete colourless colonies.

G. The staphylococcus grows well and freely upon blood agar. After twenty-four hours at 37° C. it appears as an opaque yellowish paint-like growth spreading out from the track of inoculation. On further incubation it grows into the medium, producing a yellowish brown discoloration.

The diplococcus grows well on blood agar. After twenty-four hours' incubation the colonies appear as distinct, clear, and almost colourless growths along the track of inoculation On further incubation the colonies increase in size, but do not form a continuous film unless present in great numbers. In time they produce a change of colour, and the red brown of the blood agar is changed into a yellow brown where the micrococci grow down into the medium. The alteration is very similar to that produced by the pneumococcus.

H. Both micro-organisms grow in alkaline litmus milk, but the diplococcus usually produces more acid, and a firm clot ; the *Staphylococcus aureus* less acid and a looser clot.

In 1901 Triboulet and Coyon showed that the diplococcus produced formic acid in nitrogenous media, and acetic acid in milk. In this treatise[1] they give a careful account of various acids which they have found during the growth of the micro-organism. The production of formic acid has been fully confirmed by Dr. Ainley Walker and Mr. Ryffel.[2] And for us Mr. George Berger of King's College, Cambridge, has demonstrated that acetic acid is especially formed in the milk medium, confirming again the observations of Triboulet and Coyon.

It is clear then that with care these two micro-organisms can be differentiated from one another.

We next come to these all-important questions : Is the *Staphylococcus aureus* an organism which is present in cases of undoubted rheumatic fever, and can it be isolated from the local lesions ? Our experiences and those of Dr. Paine have been very definite, for we have not found this micro-organism,

and although we do not pretend that we have always obtained pure cultures in our investigations, yet when we failed to do so we did not find the *Staphylococcus aureus* as the cause of the mixed culture. Needless to say, we attach great importance to this evidence, which appears to us to have a vital bearing on the pathogenesis of rheumatic fever.

Further, though each one of us has isolated the *Staphylococcus aureus* from the human tissues, the conditions we have found in such cases were not to be confused with those of rheumatic fever, when it was possible to make the investigation complete, but if the investigation is incomplete it is easy enough to fall into error. It is, for example, within the experience of all that the *Staphylococcus aureus* may cause an arthritis or pleurisy, which need not reach the stage of suppuration, and which clinically cannot be distinguished from the rheumatic inflammation. So also the tubercular infection may sometimes cause these same fleeting inflammations.

But we do not call these conditions "pseudo-rheumatism," much less rheumatic fever. Again, because we usually meet with staphylococcic arthritis in the suppurative stage, and rheumatic arthritis in the non-suppurative stage, we do not think it correct to argue that the rheumatic arthritis is an attenuated variety of the staphylococcal. The tubercular, pneumococcic, staphylococcic, and other infections show different grades of virulence and these assist in producing the differences in the clinical course of the diseases which result. We expect the same to occur with the rheumatic infection, and believe that it does occur, although its recognition is obscured by the use of such adjectives as rheumatoid, septic, or malignant. All the great infectious diseases show their different types of virulence, but for some reason or other when this power is claimed for the rheumatic, it is often objected that rheumatic fever is not really a disease at all but only a peculiar reaction to many infections.

Our position is not based on mere theory. There is the evidence of clinical observation, such as Dr. Paine and Dr. Poynton put forward in a paper upon malignant endocarditis, published in the *Medico-Chirurgical Transactions* in 1902. There is also the experimental proof put forward upon that occasion. We will give a further experimental proof with the diplococcus kindly sent to one of us (W. V. S.) by Professor

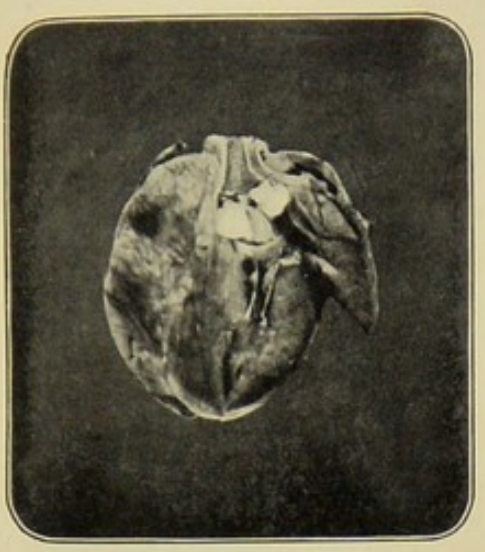


FIG. 69

Heart of a monkey. The left ventricle is laid open and the mitral and aortic valves exposed. Vegetations of considerable size are seen on each segment of the aortic valve. Minute vegetations are also present on the mitral valve. The result of intravenous injection of the *Diplococcus rheumaticus.*

FIG. 70

The heart of a monkey. The left ventricle is laid open and the mitral valve exposed. There are vegetations on the mitral valve and pyæmic abscesses in the myocardium. The result of intravenous injection of the *Staphylococcus pyogenes aureus* and the *Diplococcus rheumaticus.*

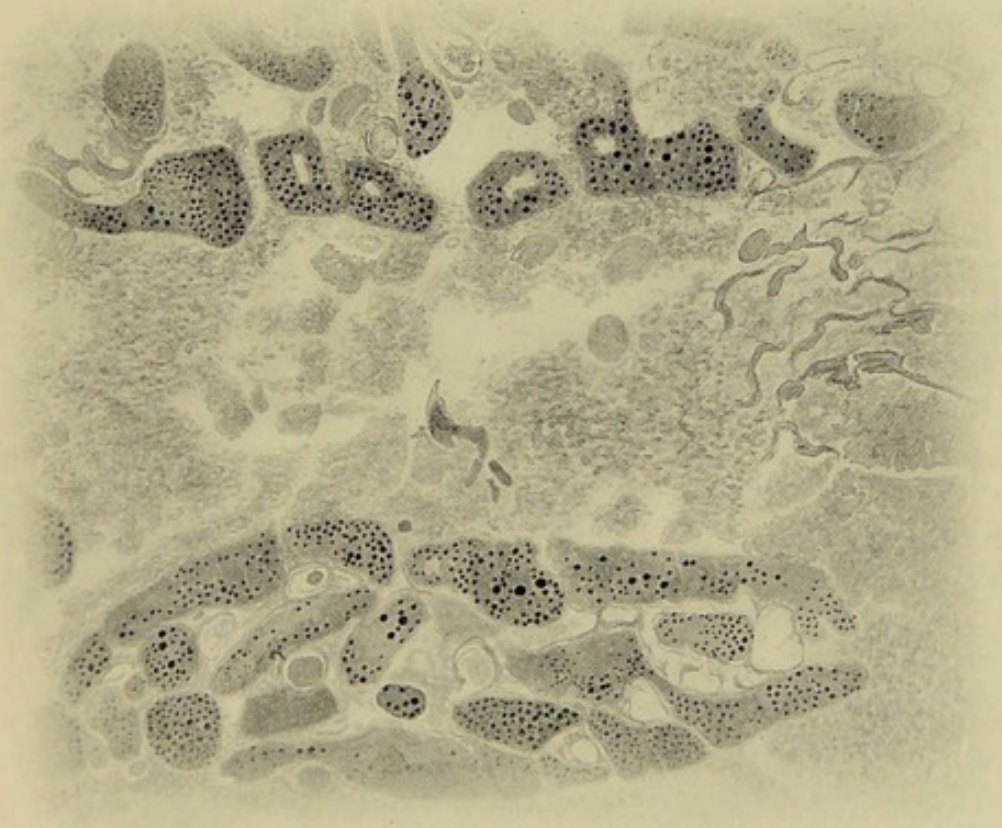


FIG. 71

Section through the myocardium of the heart (Fig. 69) showing fatty degeneration. (Zeiss, obj. $\frac{1}{12}$, oc. 4.)

Wassermann. It was obtained from a case of fatal chorea and rheumatic fever. This micro-organism produced in different animals these differing results : a transitory arthritis ; an arthritis with endocarditis and infarcts in the lungs, kidneys and spleen ; and an acute illness fatal on the third day, with early endocarditis and arthritis.

Thus it must be admitted that rheumatic fever may cause something more than fleeting inflammation.

But, although we have not demonstrated the *Staphylococcus aureus* as a cause of rheumatic fever, it must needs be that our investigations have not been very numerous. Taking into account the earlier work of Dr. Paine and Dr. Poynton, some twenty-five fatal cases of rheumatic fever form the basis of this investigation, and compared with the frequency of the occurrence of the disease, these only represent a small total. It may be objected, then, that this evidence is insufficient, and for this reason we have further studied the experimental results produced in rabbits by the *Staphylococcus aureus* in pure culture.

Before dwelling upon these experimental results we should like to protest against that attitude of mind which expects that a micro-organism should produce infallibly a constant result in animals. Pathogenic organisms are not always pathogenic to man, nor do they always when they are pathogenic produce a regulation disease ; the same is equally true of animals. Our excuse for this obvious remark must be this, that from time to time the objection is brought forward that the results of inoculation of animals, especially rabbits, are quite unreliable. That has not been our experience, and we are convinced that, if the disease in the animal is studied as the disease in man, a definite conclusion can be arrived at, so far as rheumatic fever is concerned.

The experimental results from the inoculation of the *Staphylococcus aureus* are well known, but we have repeated them again, and one of us had already repeated them with Dr. Paine[3] with the special object in view of producing conditions similar to those which result from inoculation of the diplococcus of rheumatic fever. Since one of us (.W. V. S.) has recently recorded[4] the results of inoculation of the diplococcus into monkeys we have been able to amplify this part of the investigation in a direction which is of considerable interest, and which has strengthened our belief in the entity of rheumatic fever.

The result of intravenous inoculation of the *Staphylococcus aureus* into rabbits is in the vast majority of cases to produce : (1) septicæmia and rapid death without local lesions but with much hæmolysis ; or (2) pyæmia with abscess formation in the kidneys, spleen, heart-wall or elsewhere ; or (3) no result at all.

If, instead of intravenous inoculation, an injection is made locally into such a joint as a knee-joint, the illness is more gradual, but abscesses form in the various organs, and in rare cases endocarditis of the ulcerative type may occur.

The micro-organism can be easily recovered from the blood in which it produces great hæmolysis, and, speaking generally, the tendency of the disease is to produce either a fatal result or no effect.

The usual results of the inoculation of rabbits intravenously with the diplococcus are as follows : After an incubation period of about one to three days, during which time the animal may show a rise of temperature, the heart becomes excited, arthritis develops in one or more joints, especially those of the knee and carpus, mitral endocarditis, pleuro-pneumonia and pericarditis may follow, and the animal as a rule dies from the cardiac inflammation. Nodules, choreiform movements, hæmorrhages, iritis and nephritis have been noticed in exceptional cases. We have never met with an abscess in the kidneys, spleen, liver or heart-wall, but have observed white infarcts in the kidneys. The duration of the illness varies, but if it is fatal, death usually occurs between seven and twenty-one days. Recovery is not uncommon, and this after very definite symptoms of the infection have developed ; or again, chronic articular inflammation with osteo-arthritic changes may result and persist for months, the animal having otherwise recovered. The endocarditis may affect the mitral, aortic or tricuspid valve, but with by far the greatest frequency the mitral is the one attacked.

It may be a simple or a vegetative endocarditis, and every grade between these can be demonstrated. Septicæmia we have not seen, even with large injections, but a negative result is not uncommon after small injections.

The diplococcus can be recovered in pure growth from the advanced exudations, but not with certainty from the blood.

When a monkey has been injected intravenously the following symptoms have been observed by one of us (W. V. S.), and

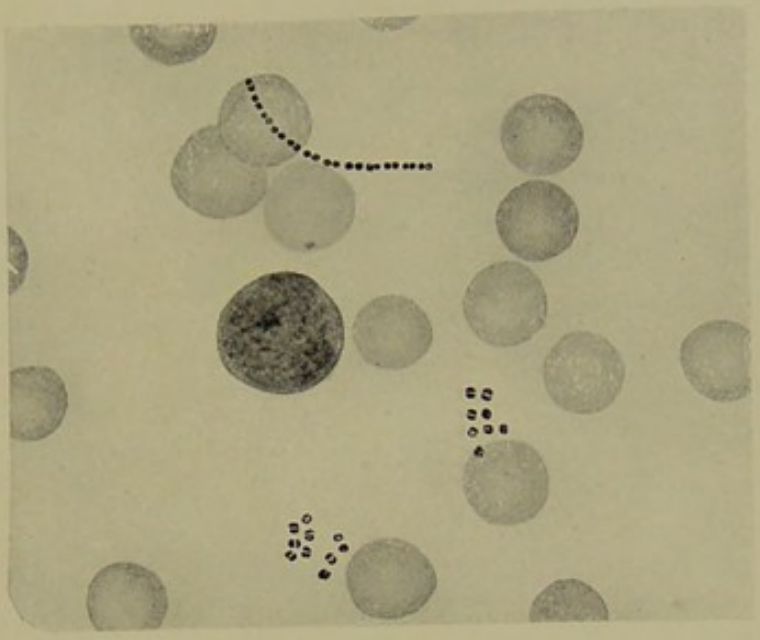


FIG. 72

Blood film from a monkey dead from the intravenous injection of the *Diplococcus rheumaticus* and the *Staphylococcus pyogenes aureus*. The film shows the diplococcus in chain form, the staphylococcus in clusters. Both micro-organisms were isolated from the tissue. (Zeiss, obj. $\frac{1}{12}$, oc. 12.)

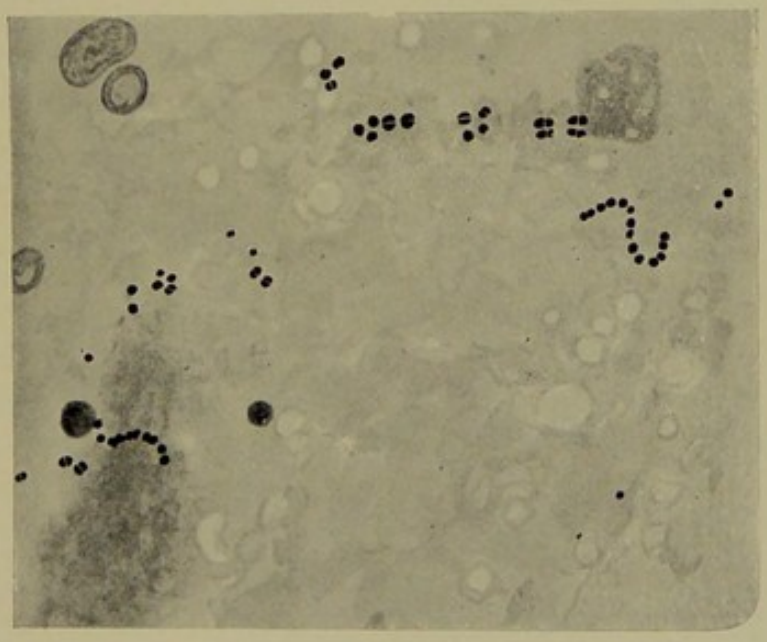


FIG. 73

Experimental arthritis (mixed infection). A film from the exudation into the knee-joint of a monkey dead from the simultaneous intravenous injection of the *Diplococcus rheumaticus* and the *Staphylococcus pyogenes aureus*. Both micro-organisms are present in the film, the diplococcus in chains, the staphylococcus in groups. (Zeiss, obj. $\frac{1}{12}$, oc. 12).

were published in the *Journal of Pathology and Bacteriology* for December 1903.

1. In one case a transient arthritis supervening about twelve hours after infection.

2. In another, a multiple arthritis followed by pericarditis, endocarditis, and myocarditis. The exudations were sero-fibrinous ; there were also hæmorrhagic infarcts found in the kidneys ; there were some patches of broncho-pneumonia and enlargement of the spleen. Death occurred on the fourth day.

3. In a third case, multiple arthritis of much severity followed infection, and later a mitral systolic murmur developed, but the animal made a good recovery, and is still alive four months later.

The diplococcus can be recovered in pure growth from the exudations.

We are of opinion that anyone who makes an experimental study of these two micro-organisms, or who, failing this, trusts to the evidence of repeated observation by others, must conclude that the weight of experimental investigation, even when divorced from clinical observation, is opposed to the acceptance of the *Staphylococcus aureus* as a cause of rheumatic fever.

In these investigations of ours care was taken to put these two bacteria under the same conditions out of the body, and to use them in varying degrees of virulence. We are thus convinced that there is a wide difference in the nature of the two infections.

But there is another problem connected with the *Staphylococcus aureus :* Can this micro-organism produce a disease indistinguishable from rheumatic fever if that infection is a mixed one ? The clinical study of these mixed infections is one of the greatest difficulty, and at the present time it is almost impossible to judge of the relative parts taken in a disease by two infective agents. It is possible, nevertheless, that something may be learnt from an experimental study of this problem, especially if clinical facts can be steadily accumulated for comparison with such investigations. The two micro-organisms we are studying in this paper give, as we have shown, very different experimental results, and so we have tried the effect of the injection of mixed cultures simultaneously, and the effect also of the injection of the *Staphylococcus aureus* after previous infection with the diplococcus of rheumatic fever.

The animals we have used have been rabbits and monkeys. To make a brief summary of our results :. we found in the first place when the injections were simultaneous that the presence of the *Staphylococcus aureus* impressed itself by rendering the disease unlike rheumatic fever and like pyæmia, and that this, the more virulent organism, caused us special difficulty in making observations, because the death of the animals was often very rapid. If the animal had already shown signs of rheumatic fever, then the staphylococcus killed it with the evidences of septicæmia and abscess formation. The effect of simultaneous injection with both micro-organisms was well shown in the case of a monkey. Death occurred on the fifth day. During this time extensive arthritis developed, with a fibrinous exudation, containing the diplococcus in great numbers. There was mitral endocarditis, and in addition there were pyæmic abscesses in the heart-wall containing vast numbers of the *Staphylococcus aureus*. The staphylococcus and diplococcus were present in the blood. Both micro-organisms were isolated again after death, the diplococcus from the arthritic exudation and the *Staphylococcus aureus* from the blood.

With rabbits also, it was our experience that the diplococcus was most easily found in the joints, and the *Staphylococcus aureus* in the blood, and that the type of the disease was pyæmic. Both micro-organisms were again isolated from the animal tissues. In the solid tissues it is hardly possible, we believe, to differentiate the two micro-organisms under the microscope, for, although the diplococcus is more easily decolorised by Gram's method, that is a comparative test difficult to apply in the tissues. In the exudations the streptococcal arrangement of the diplococcus is helpful, and the occurrence of the staphylococcus in masses in the pyæmic abscesses is also characteristic.

Our preparations will show that it is possible to differentiate the two micro-organisms in the fluid tissues and by culture, but so far as a solid tissue is concerned—for example, a mitral valve—we hesitate to state dogmatically that the micro-organism present is the diplococcus or staphylococcus, or whether both are present in the lesion.

We have alluded to the rapid deaths of the animals from the presence of the *Staphylococcus aureus*. This we endeavoured

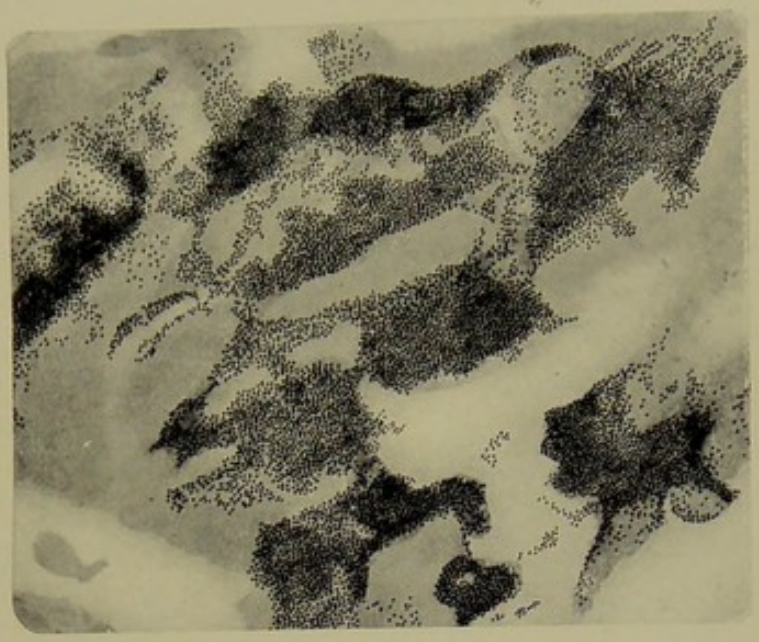


FIG. 74

A section through a pyæmic abscess in the myocardium of a monkey dead from the simultaneous intravenous injection of the *Diplococcus rheumaticus* and the *Staphylococcus pyogenes aureus*, showing great numbers of the *Staphylococcus aureus* in the necrotic tissue, from the same animal as the preceding. Death resulted on the fourth day from pyæmia. Both the micro-organisms were recovered from the tissues. (Zeiss, obj. $\frac{1}{12}$, oc. 4.)

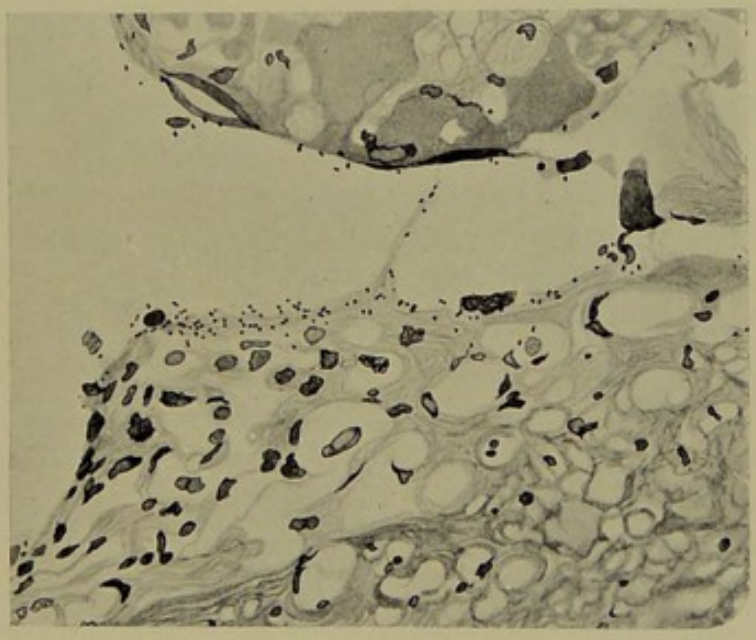


FIG. 75

Experimental endocarditis (mixed infection). Section through a minute vegetation on the mitral valve of the heart of a monkey. The vegetation shows the structure of the ordinary rheumatic form, and the arrangement and appearance of the micrococci lead to the belief that this was a rheumatic lesion. (Zeiss, obj. $\frac{1}{12}$, oc. 2.)

to overcome by inoculating mixed cultures directly into the knee-joints of rabbits.

The animals then survived a longer time, but as before developed pyæmia with abscesses in the liver and spleen. Again the diplococcus was found most easily in the arthritic exudations, the *Staphylococcus aureus* in the blood and spleen.

We conclude, then, that the *Staphylococcus aureus*, when injected into these animals in association with the diplococcus, tends to alter the type of the disease from that of rheumatic fever to that of pyæmia and staphylococcic septicæmia.

This conclusion, so far as one can apply it to clinical medicine, upholds our opinion that rheumatic fever is not a result of the staphylococcic infection, and should a staphylococcic infection supervene upon the rheumatic the tendencies would be twofold :

1. To accelerate death.
2. To produce a condition of pyæmia rather than malignant endocarditis.

Our clinical opportunities of studying mixed infections have been few, but in 1901 Dr. Paine and Dr. Poynton had the opportunity of studying such a case in a child.

A boy aged 8¾ years was admitted on February 15, 1901, to the Hospital for Sick Children, Great Ormond Street, suffering from cellulitis of the right leg, the result of a sore on the heel. The limb was incised, but no pus escaped. Three days afterwards he complained of pain in the right hip, and the next day of pain in the left hip. Upon the 24th loud pericardial friction was heard, and upon March 1, there was pain in the left shoulder.

Several who saw this child, though well acquainted with the fact of the cellulitis, suspected that this illness might be rheumatic fever because of the low range of temperature, the absence of shivering and rigors, the slight distress, and the loud pericardial friction. The child died on March 4, and at the post-mortem there were found purulent pericarditis and arthritis, with abscesses in the kidneys and lungs. Dr. Paine took cultures from the pericardium and left hip-joint. In each case the result was a mixed one of the *Staphylococcus aureus* and a minute diplococcus. This case exemplifies the point we emphasised earlier—the importance of a complete investigation. Many of the clinical features of the case resembled those of rheumatic fever ; the necropsy showed

conclusively that it was not rheumatic fever. The bacteriologist demonstrated it to be a mixed infection, and the *Staphylococcus aureus* as a cause of the pyæmic condition.

We put forward, then, these two statements based on this investigation :

(1) The *Staphylococcus aureus is* not a cause of rheumatic fever either in simple or mixed infection.

(2) Rheumatic fever is not an attenuated pyæmia, so far as the *Staphylococcus aureus* is concerned.

REFERENCES

[1] " Le Rheumatisme Articulaire aigu."

[2] " On the Pathology of Acute Rheumatism and Allied Conditions," *Brit. Med. Journ.*, September 19, 1903.

[3] " A Contribution to the Study of Malignant Endocarditis," *Med.-Chir. Trans.*, 1902.

[4] *Journal of Pathology and Bacteriology*, December 1903.

PART II

SUB-GROUP D

THE GREATER PART OF THESE PAPERS IS DEVOTED TO THE ELUCIDATION OF SOME OF THE IMPORTANT NERVOUS MANIFESTATIONS OF ACUTE RHEUMATISM. WE WERE FORTUNATE ENOUGH TO OBTAIN THE COLLABORATION OF DR. GORDON HOLMES IN ONE OF THEM DEALING WITH THE MINUTE PATHOLOGY OF CHOREA

IN THIS SUB-GROUP SOME SPACE HAS BEEN GIVEN TO ANSWERING THE CRITICISMS OF OUR PREVIOUS RESULTS, WHICH HAD STEADILY ACCUMULATED. IT WOULD HAVE BEEN AN INJUSTICE TO OUR CRITICS AND TO OURSELVES IF WE HAD NOT RETAINED THIS PART OF THE WORK, WHICH HELPS, WE FELT, TO SHOW THAT WE DID NOT OVERLOOK SUCH CRITICISMS BUT ATTEMPTED TO MEET THEM BY FURTHER INQUIRY. THIS DUTY WAS THE MORE IMPERATIVE BECAUSE THE SUBJECT THAT WE DEAL WITH IS ONE OF MUCH INTEREST AND GENERAL MEDICAL IMPORTANCE

PAPER NO. XVIII

SOME INVESTIGATIONS ON THE NERVOUS MANIFESTATIONS OF ACUTE RHEUMATISM [1]

(Reprinted from the *Lancet*, December 1905.)

The first part of this paper is mainly retrospective, and concerned with answering criticisms raised by our previous communications. The second part brings forward some new facts bearing upon the pathology of rheumatic chorea. The third deals with a very remarkable case of cerebro-spinal meningitis following upon a mild attack of rheumatic fever. This paper was read at a meeting of the Neurological Society of the United Kingdom, with the intention of inviting discussion upon the case of cerebro-spinal meningitis, but unfortunately there had been a desire expressed to throw open the entire question of the ætiology of acute rheumatism, with the result that no further light was thrown upon this particular case. We have published it again here, for the bacteriological investigations that were undertaken to differentiate the diplococcus from the pneumococcus were prolonged and minute, and resulted in the conviction in our minds that the meningitis was not due to a secondary pneumococcic invasion.

Dr. Beattie in 1904 *had published the first of his numerous investigations upon the cause of acute rheumatism, which have supported our investigations and added new facts to the subject.*

We commence this paper by putting forward our present attitude towards the ætiology of acute rheumatism and answering some of the objections that have been raised against our interpretation, for we feel that if we do not take this precaution the particular points bearing upon the nervous system which are the subject of this paper will seem to rest upon an insecure basis.

Part I.—The Ætiology of Acute Rheumatism

Five years ago in a paper published in the *Lancet* [2] we claimed that we had proved that a diplococcus was a cause of

rheumatic fever—a cause that had been hazarded by others in England, Germany, and France before the publication of our article.[3] Two years later before the Royal Medical and Chirurgical Society [4] we showed that rheumatic fever might be a cause of malignant as well as so-called simple endocarditis. Since then and up to the present time we have been gradually filling in the gaps in our knowledge and strengthening the weaker links in the chain of proof. Our position now has not altered : we still firmly maintain that this diplococcus is a cause of rheumatic fever ; and further, we believe it to be the only bacterial cause ; we also maintain that rheumatic fever is a cause of malignant endocarditis.

These views clearly imply that we hold that there is a definite disease—rheumatic fever. We do firmly believe this and hold that it is as definite a disease as tuberculosis. There are, admittedly, cases of rheumatic fever that are most difficult to differentiate, but they are no more numerous or more puzzling than are difficult cases of tuberculosis or typhoid fever. These views imply, too, that we have satisfied Koch's postulates. We believe that we have done so, and at various societies in London and at the International Congress in Madrid [5] we have demonstrated the micro-organism, its pure cultures, and its presence in the human and animal tissue damaged by rheumatism. We have isolated it now from 32 cases of undoubted rheumatic fever and the disease can be produced not only in rabbits but, as Dr. Vernon Shaw [6] has shown with one of our cultures, in monkeys also.

On the other hand, we have never maintained that this diplococcus was specific except in so far that it is, in our opinion, *the only bacterial cause of a specific disease.* We set ourselves to prove that it was a cause of a specific disease and left for future investigation the next step—the demonstration of a distinctive laboratory test for the micro-organism. A very different undertaking this one, yet only too often confused with the first ; indeed, we venture to put this question prominently forward : Does a demonstration of a bacterial cause of a disease demand the demonstration of a specific test for the bacterium ?

We named the micro-organism the "diplococcus rheumaticus"—a name which has aroused a little criticism. Yet it is a reasonable and accurate name and for these reasons, in

our opinion, the best name. It is reasonable because the bacterium is a cause of rheumatic fever, and it is accurate because a diplococcus expresses the usual appearance of the micro-organism. Some hold that the name is badly chosen, because it implies that the micro-organism is specific, but clearly it in no way interferes with the appearance on the scene of a spirochæte or trypanosoma rheumaticus. Others hold that it is badly chosen because the adjective "rheumaticus" implies that rheumatism is a definite disease; our answer to this is that acute rheumatism or rheumatic fever is a definite disease, and that if the term rheumatism has any accurate meaning it should have one corresponding to that which the term tuberculosis bears in relation to acute tuberculosis or tuberculous fever.

There are some who believe that rheumatic fever is not the result of an infection. They ought, we think, to demonstrate some non-infective cause and then to explain the coincidence that a bacterium, which has been found in the arthritis, endocarditis, pericarditis, subcutaneous nodules, pleurisy, pneumonia, peritonitis, and nephritis of rheumatic fever, is able to produce similar lesions in animals. Should they look upon all these lesions as complications they should define rheumatic fever when these lesions are put aside as epi-phenomena. Many more believe that rheumatic fever is a result of many different infections. If one other micro-organism even can be said to have fulfilled Koch's postulates with reasonable constancy some one should bring forward the evidence in its favour by a clear and decisive demonstration. Lastly, there are others who believe rheumatic fever is a definite disease and that it is infective, but that the infection has not yet been demonstrated. This view naturally implies that the evidence in favour of this diplococcus is not convincing.

It is not convincing in the opinion of some because the diplococcus is not constantly present; indeed, they would go further and say it is generally conspicuous by its absence, or if it is present that it is only found after death. These objections we can only meet by a counter-statement, to the effect that it is found ante-mortem and post-mortem and that in suitably chosen cases it is found with remarkable constancy. We have ourselves found it in 32 cases and many others have isolated a diplococcus in acute rheumatism, notably, Ainley

Walker [7] and Beatson, Beattie [8] and Vernon Shaw in this country, von Leyden,[9] Triboulet, and Coyon,[10] Wassermann,[11] Predtetschensky,[12] Meyer,[13] Singer,[14] Allaria,[15] Jarvis,[16] Cole,[17] Longcope,[18] and Herry.[19]

Never easy to find, it is very difficult to discover if searched for, as it was searched for by Philipp,[20] in unlikely places such as the blood and arthritic exudations. The micro-organism multiplies and flourishes in the local lesions and the blood stream is only a channel of conduction; further, rheumatic septicæmia, as clinical experience teaches us, is rare, although two such instances have occurred in our experience. Apart from these very exceptional instances we have several times isolated it from the blood ante-mortem but the blood stream is certainly not a favourable site from which to isolate the micro-organisms in an ordinary case of acute rheumatism. Another unlikely place is the arthritic exudation, because the micrococci are deposited in the areolar tissue below the free margin of the synovial membrane and the cells lining the synovial cavity are phagocytic. Not only this, numerous leucocytes also escape into the synovial tissues and aid in the destruction of the micrococci. Then, again, the amount of exudation is comparatively small and the exudate itself containing leucocytes and endothelial cells will destroy the bacteria. If these reasons are not sufficient we would add that rheumatic arthritis is the most easily overcome of all the lesions and that in animals which have been experimentally inoculated with the diplococcus and in which as a result arthritis has developed we may fail to isolate the micrococcus from the fluid when this arthritis is in the early stage. This has happened to us repeatedly. It is of considerable interest also, as bearing upon this point, that antitoxic sera free from bacteria may sometimes produce effusion into joints and this makes it very probable that the poisons formed by the diplococci in the synovial tissue can of themselves produce an effusion into the synovial cavity. Dr. Beattie has kindly sent us a note from a further research which he has not yet published of a case in which he found in a man dead from rheumatic fever that the exudation was sterile but the congested areas of the synovial membrane, removed with all precautions, gave a pure growth of the diplococcus. This is a most striking independent proof of our assertion.

Although, then, the arthritic exudation is not a fluid in which it is easy to find the diplococcus, yet it can be found, and has been found, by ourselves and others both ante-mortem and post-mortem. On the other hand, it can only be a fair question, if we maintain that the micro-organism can be found in suitable cases with remarkable constancy, to ask what are the suitable cases? They are acute and severe ones, in which the lining membranes of the serous cavities are greatly damaged or in which the type is malignant. Sero-fibrinous pericarditis and malignant cases of rheumatic endocarditis are excellent examples. We have only failed once in recent cases of fatal pericarditis when adhesions have not been extensive and in that case we had to deal with a hæmorrhagic exudation.

A good deal of criticism has been devoted to the nature of this micro-organism; this criticism is of secondary importance. Whether or not the diplococcus is a cause of rheumatic fever is clearly of first importance, but whether or not it is an altered streptococcus pyogenes is of secondary importance because no one can define the streptococcus pyogenes. This line of criticism, however, needs a few words of comment. Take, for example, an admirable and recent investigation by Rufus Cole. Rufus Cole, having isolated a diplococcus from a case of rheumatic fever, proceeded to work as others, including ourselves, had done, with various streptococci isolated from conditions which were certainly not rheumatic, and thus concludes: "Arthritis and endocarditis may be produced by the intravenous inoculation of rabbits with streptococci from various sources, and the results are quite similar to those described as resulting from the inoculation of the so-called micrococcus or diplococcus rheumaticus." Can anyone, we ask, say that lesions are quite similar until they can explain the details of the chemical processes which have produced them? Could we venture to dogmatise upon the exciting cause of an early arthritis or endocarditis in man by looking at the lesion with the naked eye or even under the microscope? Could we, for example, say this is gonococcic, rheumatic, penumococcic or influenzal or staphylococcic?

Not, however, content with this conclusion, investigators working on these lines go further and say that the rabbit is quite useless as a test, for you can produce arthritis and

endocarditis in it with various micrococci and the occurrence proves nothing. They forget monkeys as well as rabbits are susceptible to the rheumatic infection and the fact that the first two of Koch's postulates must be satisfied—you must find the organism in the human disease you are studying and isolate it from the lesions. No one has yet claimed that at present these two postulates can be ignored in studying the cause of rheumatism and it is obviously impossible to do so until the specific test for the bacterium has been discovered. Then is it so remarkable that the rabbit is susceptible to many causes of arthritis and endocarditis. Is rheumatism the only cause of these conditions in man? Have not we heard, for instance, of gonorrhœal, staphylococcic, meningococcic, pneumococcic, scarlatinal, tuberculous and influenzal endocarditis and arthritis, yet is it quite useless to attach any importance to endocarditis and arthritis as evidences of rheumatism in man?

Another statement we have frequently heard is to the effect that this diplococcus is only an attenuated streptococcus pyogenes. Surely this is a confession of lack of clinical knowledge. Could anyone who has thoroughly studied acute rheumatism believe it to be the result of any attenuated process? It is remarkable, too, how pyæmia has disappeared since the antiseptic treatment of wounds has been introduced and yet rheumatic fever cannot be said to be any less common. What is to be said of the scientific value of that widespread doctrine that salicylate of sodium is a test of rheumatism? We think that it assumes too much that is at present unknown.

The great difficulty at the present time is, then, to find a specific test or specific tests for this diplococcus by which we can recognise it from other streptococci and it is a difficulty that will probably test the most skilful bacteriologists and chemists. Gram's stain and morphological and cultural characteristics do not carry the weight they did; bacteriology is getting older and is more cautious with its use of the word "specific." We, however, maintain that a failure to find a specific laboratory test in no way alters the conclusions that the bacterium is a cause of acute rheumatism or that acute rheumatism is a specific disease. The best test of a bacterium, though not the most practically useful one, is the satisfaction of Koch's postulates. We should not like it, however, to

be thought that we have neglected to attempt a differentiation ourselves, or have not appreciated the efforts of other investigators in this direction.

The diplococcus has, in our opinion, these peculiarities:

1. Morphologically, it is minute and smaller than the streptococcus pyogenes. The diplococcal arrangement in early cultures is more constant and it does not retain Gram's stain so well. Lastly, it resists drying in the most remarkable way for six months or even longer, which we believe is very different from the character of the streptococcus lanceolatus.

2. Physiologically, it causes an early production of acid and a greater production of acid than the streptococcus pyogenes. On this account it produces a firm clot in milk. The diplococcus will grow in a filtered culture of the streptococcus pyogenes. Ainley Walker and Ryffel [21] in a most interesting research have demonstrated that a considerable amount of formic acid is produced by, and in, these bacteria. Allusion, too, must be made to a recent paper by Gordon in the *Lancet* [22] upon a ready method of differentiating streptococci by their ability to decompose various chemical compounds belonging to the carbohydrate, glucoside, and polyatomic alcohol series, in each case with an acid reaction. No direct reference is made to the streptococcus of rheumatism, but the general conclusion of this investigator is interesting. He writes: "The chief object of my paper is to show that the individuality of streptococci is real, not apparent."

3. Experimentally, rabbits are more resistant, and arthritis and endocarditis are much more constant. It is also difficult to raise the virulence. When it produces rapid death in a rabbit we have not observed that remarkable softening of the tissues and staining of the blood-vessels seen in severe streptococcus pyogenes infections. And we have never seen abscesses in the kidneys, heart wall, spleen, or liver.

These may be small points and are certainly far from specific tests, but taken together they have, we believe, some value. It certainly seems to us that the most satisfactory working theory at present is to look upon rheumatism and its allies as one looks upon a group of chemical elements, such as chlorine, bromine, iodine, and fluorine—that is to say, there is much in common among them, yet each constituent of the group is in itself peculiar. To summarise, we hold that there

is a great infective process, the rheumatic, to be placed among that series of infective processes where the staphylococcus, streptococcus, pneumococcus, and gonococcus are to be found, and that the infective agent is a diplococcus with, in all probability, some peculiar characters.

Part II.—Chorea

Passing now to the particular investigations which prompted us to write this paper, the first have reference to chorea. In May 1901, in a paper in the *Lancet*, we elaborated in some detail the view that rheumatic chorea was a result of the diplococcus infection. We speak advisedly of rheumatic chorea, not being prepared to maintain that all chorea is rheumatic, for it may be that other infections, especially of the streptococcal group, can also sometimes produce this condition and many also believe that fright is an exciting cause. With regard to this latter point, as a result of personal inquiry into the history of 250 cases of chorea under 12 years of age, we support Dr. D. B. Lees's opinion that fright, as an exciting cause, is greatly overrated, but we believe that it is, as many authorities have long maintained, a predisposing one of importance. It hardly need be said that we believe implicitly in the teaching of those who have held that the great majority of cases of chorea are rheumatic, and rheumatic in the sense that the chorea is an actual manifestation of the disease. Here, again, we would submit that the clinical evidence in favour of this view is overwhelming.

If then, for the moment, the diplococcus is accepted as a cause of rheumatic fever, the first essential in the explanation of rheumatic chorea is to bring forward evidence of its presence in the nervous system or general circulation when the rheumatism is active and has been the cause of death. Such evidence is slowly accumulating. Thus a diplococcus was isolated under such conditions by Dana [23] in 1894 and again in 1898 by Apert,[24] who then distinctly stated that he thought it was identical with the diplococcus discovered by Triboulet and Thiroloix in aggravated rheumatic fever. In 1889, Westphal, Wassermann, and Malkoff published their important case of a child, dead from rheumatic pericarditis and chorea, from whose pericardial and cerebro-spinal fluids was isolated a

diplococcus which produced arthritis in a series of 80 rabbits. These observers maintained that this diplococcus was the cause of acute articular rheumatism. In 1900 we recorded the occurrence of choreiform movements in a rabbit as a result of an intravenous inoculation of the diplococcus, and in 1901 we verified the occurrence of a diplococcus in the cerebro-spinal fluid of a child who had died from severe rheumatism with chorea. Fritz Meyer, in 1901, with a diplococcus obtained from rheumatic angina faucium, produced irregular choreiform movements in six rabbits. In 1903 Beaton and Ainley Walker twice isolated a diplococcus post-mortem from the heart's blood and once ante-mortem from the urine in rheumatic chorea, and in two of these cases produced arthritis and endocarditis. In 1903, at the International Congress,[25] we also brought forward a fatal case of rheumatism with chorea, in which we had isolated the diplococcus from the pericardial fluid and produced not only arthritis, as had Wassermann, but also pericarditis and endocarditis. In 1904 Beattie recorded the same occurrence with a diplococcus which he had independently isolated from a case of fatal rheumatism. In his case the diplococcus was isolated from the arthritic exudation and also produced choreiform movements in a rabbit.

Now, again, in two cases of rheumatic fever dying with symptoms of chorea we have isolated this diplococcus from the cerebro-spinal fluid. In one case the virulence of the cultures was not sufficient to produce any experimental effect; in the second case, however, not only was arthritis produced but also endocarditis and pericarditis—that is to say, a micro-organism circulating in the cerebro-spinal fluid during an acute attack of rheumatism with chorea was able to produce such lesions as arthritis, endocarditis, and pericarditis. This, we think, brings us a step nearer the elucidation of chorea, and owing to the kindness of Dr. Lees we are enabled to give a brief account of this case. A boy, aged nine years, who had suffered from acute rheumatism at three years of age, was admitted to St. Mary's Hospital under Dr. Lees on Nov. 22, 1904, in a second attack. Previously to his admission he had been ill for seven weeks with sore-throat, multiple arthritis, and general chorea, and he only lived two days in the hospital, dying with general pericarditis and violent chorea. The necropsy showed a pericardium bound down by recent and old

adhesions but there was no endocarditis. The liver and kidneys were engorged, there was pleurisy with fibrino-plastic exudation, and the brain was hyperæmic.

This, then, may be looked upon as a case of severe rheumatic fever in which chorea was a notable manifestation at the time of death. Cultures were made from the blood in the heart, the pericardial and cerebro-spinal fluids, in milk bouillon. One tube of blood from the heart was sterile and one contained a pure growth of the diplococcus, the tube with the cerebro-spinal fluid contained a pure growth, and the pericardial fluid contained the same micro-organism, together with the staphylococcus albus, from which it was separated by plate culture. Two inoculations were made from these cultures : (*a*) a small dose was injected subcutaneously into a small rabbit ; and (*b*) a large dose was injected intravenously into a large rabbit. The first developed a small inflammatory nodule at the site of inoculation, which disappeared gradually without any constitutional symptoms. The second, injected intravenously, died in 24 hours. Diplococci were present in the blood. All the organs were firm and not soft as in the case of a septicæmia from a septic infection. The diplococcus was isolated and again cultivated. Another series of cultures was then made from the original strain and three more inoculations were made on November 30. (1) A five cubic centimetre bouillon culture was injected intravenously into rabbit No. 3 ; (2) the contents of three blood serum tubes were injected intravenously into rabbit No. 4 ; and (3) the contents of three blood agar tubes into rabbit No. 5. The last of these three animals developed arthritis on the third day and died on the fifth from general pericarditis, cardiac dilatation, and mitral endocarditis. We have been asked whether we have also obtained the diplococcus from the brain but the question is impossible to answer, because one cannot exclude the possibility of either pia mater or cerebro-spinal fluid being included in the fragments.

There have been a certain number of observations pointing to the presence of the staphylococcus aureus as a cause of chorea. We have not ourselves been able to trace such a connection in rheumatic chorea and in the preceding paper by Poynton and Vernon Shaw [26] some evidence was brought forward to show that this micrococcus was not a cause of rheumatism and rheumatic chorea. Nevertheless it is quite

possible that the aureus infection may produce chorea if we admit that other infections allied to the rheumatic may be, in exceptional cases, exciting causes.

We would ask now for the acceptance of the view that rheumatic chorea is a result of the diplococcus infection, for then we can pass on to the next consideration—the nature of the morbid lesions. At the outset we are confronted with this difficulty: we know that the lesions in rheumatic fever are of the type of pyæmic lesions—that is, they are local infections of various organs—and we also know that there is a variable amount of general systemic poisoning as evidenced by the rapid anæmia. Applying this knowledge to the nervous system we have two possibilities. Chorea may be a result of local lesions comparable to other *local* rheumatic lesions, or it may be that the delicate nervous tissues are exceptionally sensitive to the *general* rheumatic poisoning. We incline to the view that chorea is a result of numerous slight local lesions, and it will be at once apparent that we are thus led to a slight modification of the original views of that illustrious neurologist, Dr. J. Hughlings Jackson. To a slight modification in that we do not suppose that there is actual embolism, but rather the occurrence of small focal lesions external to the blood capillaries caused by the escape of the diplococci which are carried by the blood stream into these positions. The local changes around the capillaries might cause hæmorrhage, thrombosis, perivascular exudation, and in chronic cases perivascular fibrosis. The poisons that are elaborated would probably cause fatty and other destructive changes in the nervous tissues themselves. We should expect the pia mater to be definitely affected in chorea because of its analogy to the other serous membranes and because there are an enormous number of minute blood-vessels in this membrane.

If, on the other hand, the general systemic poisoning is responsible for chorea one almost despairs of getting any nearer the solution of this problem until the chemistry of rheumatism is elucidated, for these general systemic poisonings are beyond the reach of morbid anatomy. Working along these lines we have attempted by intravenous injections of formic acid in rabbits to produce choreiform movements, but failed to obtain any such result. Reichart [27] has recently published accounts of a careful investigation of two brains in

cases of fatal chorea. The bacteriological investigations were negative, but in both cases he found small hæmorrhages scattered irregularly throughout the brains; there were dilatation of blood-vessels and perivascular exudation of cells. This observer also found fatty changes in the nerve fibres of the brain and cord. These are changes such as would be associated with an infection of the rheumatic type. The finding of such local lesions to some extent supports the view that chorea is a result of such changes rather than of a general cerebral poisoning by the toxins. A more convincing point in the pathology of chorea would be the demonstration of the diplococci in the pia mater or brain in cases of chorea. Our opportunities for doing this have been few. At a meeting of the Pathological Society in December 1900 [28] we demonstrated diplococci in the motor cortex of a case of very severe chorea, but most unfortunately we did not, when we made the necropsy, recognise the relation of the diplococcus to rheumatism. In both our recent cases alluded to here we found them in the pia mater as we foretold from animal experiment in 1900—viz., in the neighbourhood of the capillary blood-vessels. There is no doubt in our minds that the destruction of these diplococci in the pia mater must be rapid, for chorea is a lesion comparable to rheumatic arthritis in the tendency to complete recovery, and, as we have already pointed out, it is no easy task to find them in acute arthritis. It is, we think, encouraging to have shown a diplococcus in three consecutive cases of chorea and in the last case we know that this diplococcus can produce arthritis and pericarditis in rabbits and could be isolated from the cerebro-spinal fluid.

Lastly, a section of a mitral valve from a case of early endocarditis with very severe chorea illustrates how easily the brain could be infected from the blood stream, *vide* Fig. 64. These have been our only opportunities and neither of the last two cases should we have chosen for demonstration, for they were not essentially cases of fatal chorea but rather fatal pericarditis with chorea. During the last five years we have never had an opportunity of investigating one of the rare cases of fatal chorea. We have not attempted lumbar puncture for we cannot persuade ourselves to do this simply for purposes of investigation, and

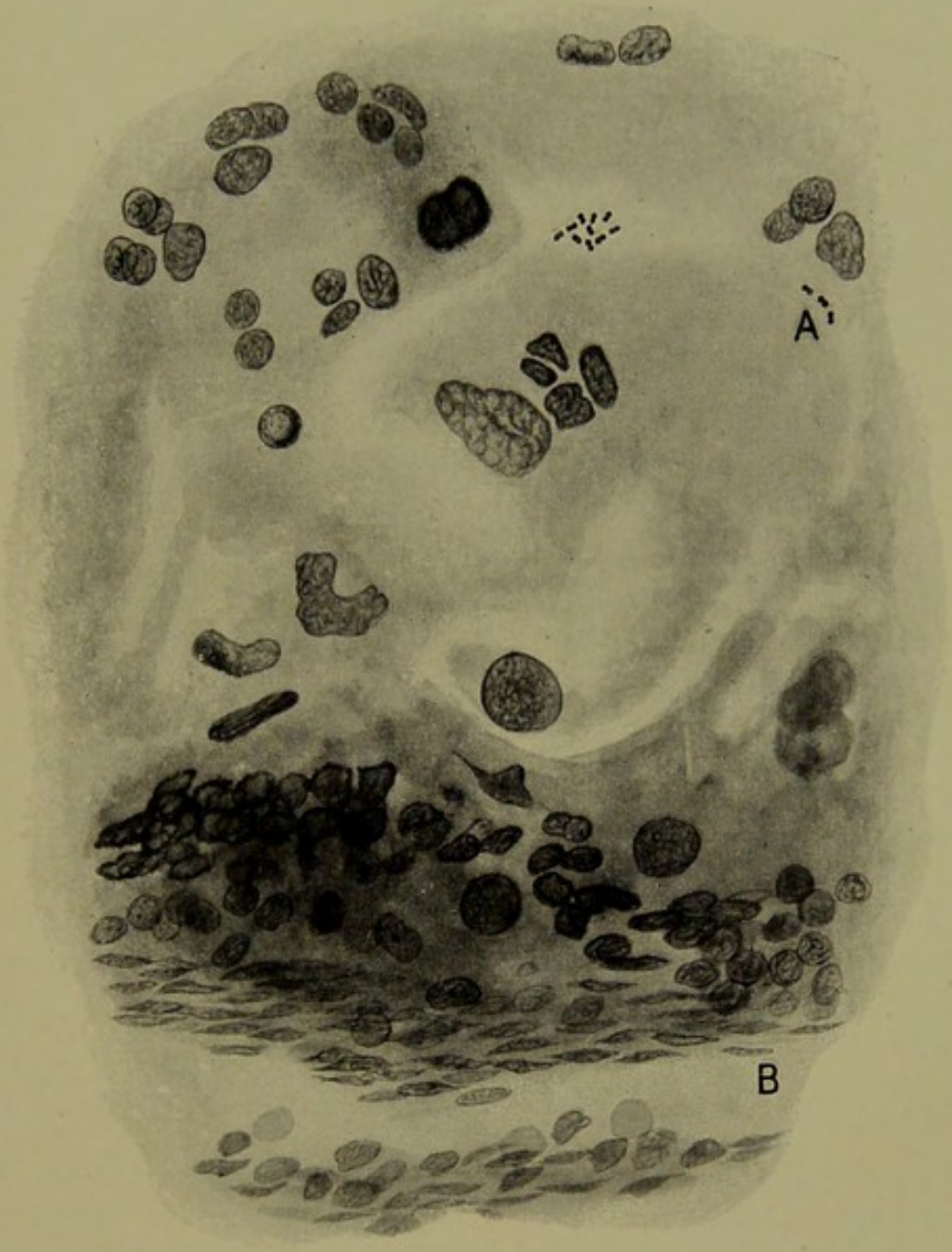


FIG. 76

Film of the pia mater showing : A, diplococci in the pia mater ; B, a capillary blood-vessel. From a case of fatal rheumatic pericarditis with chorea. (Zeiss, obj. $\frac{1}{12}$, oc. 12.)

our views upon the probability of success of this method are expressed in our views upon arthritis. In spite of this, the fact that we have succeeded in demonstrating the diplococcus in cases in which death occurred with chorea does, we believe, add another link to the chain of evidence, and it is the more suggestive because we discovered them in the pia mater near capillary blood-vessels in the rabbit which showed involuntary movements.[29]

These experimentally produced irregular movements need a passing mention. Originally described by ourselves in 1900, we then in a very guarded manner suggested that the movements in the rabbit were analogous to chorea in a child. Meyer and Beattie independently verified the occurrence and noticed twitching movements. Cole later produced twitching movements in rabbits by the injection of other streptococci and states that the movements had no resemblance to chorea. In our case the movements were of that type and entirely different from convulsive movements or the twitchings of a dying animal ; in fact, we killed the animal in order to demonstrate the diplococci in the brain or pia mater. The search, it may be added, was most tedious and difficult, as might be supposed when it is remembered how minute is the size of this diplococcus.

To summarise, we believe that eventually rheumatic chorea will prove to be a local infection of the nervous system and that most of its symptoms are the result of a slight meningo-encephalitis and possibly meningo-myelitis. Our reasons for this belief are : (1) We have isolated and cultivated the diplococcus from the cerebro-spinal fluid in four cases of fatal rheumatism, in three of which there was chorea at the time of death. (2) We have produced irregular movements, arthritis, endocarditis, and pericarditis by intravenous injections of the diplococcus into rabbits. (3) We have demonstrated the presence of diplococci three times in the cerebral pia mater and once in the brain from chorea. (4) We have demonstrated them in the brain and pia mater of the rabbit that had shown the irregular movements.

Part III.—Rheumatic Meningitis (?)

Our last case is a most interesting one. A well-made and intelligent boy, 13 years old, was admitted into University

College Hospital on August 26, 1904, suffering from arthritis of the ankles and knees and from pain across the chest upon drawing breath. The first attack of pain had occurred four days before his admission, the ankles had commenced to swell three days before, and the knees upon the day previous. The family history showed that the boy's father had suffered from rheumatic fever but the patient himself, except for an attack of measles and an operation for adenoids, had enjoyed excellent health. His condition on admission appeared to be a very ordinary attack of rheumatic fever. The temperature was 103.6° F. and the arthritis was of the usual type, the heart was dilated, and there was a definite systolic mitral murmur which was conducted to the left axilla. Further, rest and salicylate of sodium rapidly reduced the temperature and by the 30th, that is in four days, all pain and swelling had disappeared. From that date until September 17, a period of nearly three weeks, his convalescence was uninterrupted, while in order to prevent a relapse small doses of salicylate of sodium were continued. On the 17th, without any apparent cause, he complained of headache ; he was sick, and his temperature rose to 102.4° F. The next day, although better in the morning, he again vomited in the afternoon and suffered severe pain in his head. That evening he was drowsy and his temperature rose again to 102.6° F. The bowels were constipated and for this reason an enema was given, after which he collapsed and became cyanosed and almost pulseless. At 8 A.M. on the 19th he became unconscious, with fixed dilated pupils and general muscular rigidity, alternating with flaccidity. His skin, though hot, was moist ; his temperature in the axilla at 8 A.M. was 101° F., and at 11 A.M. 102.4° F. The temperature was now taken in the rectum and also twice with different thermometers in the groin and axilla. In the rectum the temperature was 106.4° F. ; in the other situations it was still 102.4° F. All efforts at treatment were fruitless and the boy died comatose at 7.40 that evening. The difference in the temperature in the axilla and in the rectum of over 4° F. is remarkable and we believe very exceptional ; in fact, if the rectal temperature had not been taken the hyperpyrexial element in the illness would certainly have escaped notice. The clinical aspect of this case was a very puzzling one, not only on this account but because the symptoms supervened without warning at a time

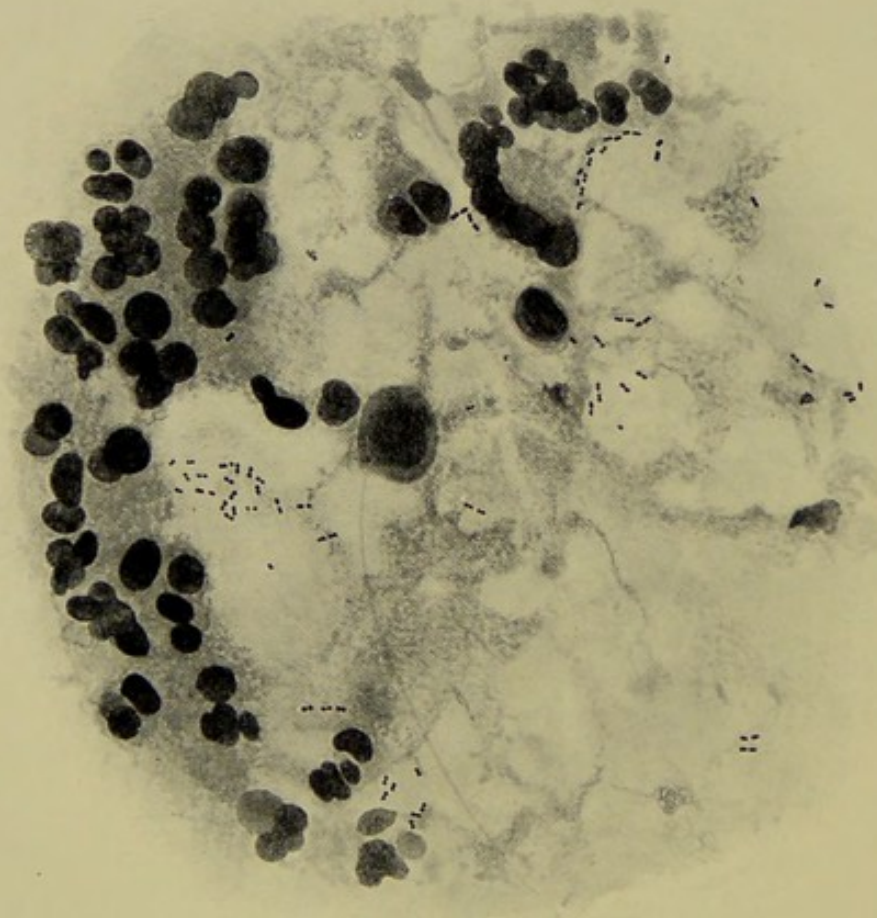


FIG. 77

Cerebro-spinal meningitis in rheumatic fever. Film from the pia mater showing diplococci. (Zeiss, obj. $\frac{1}{12}$, oc. 12.)

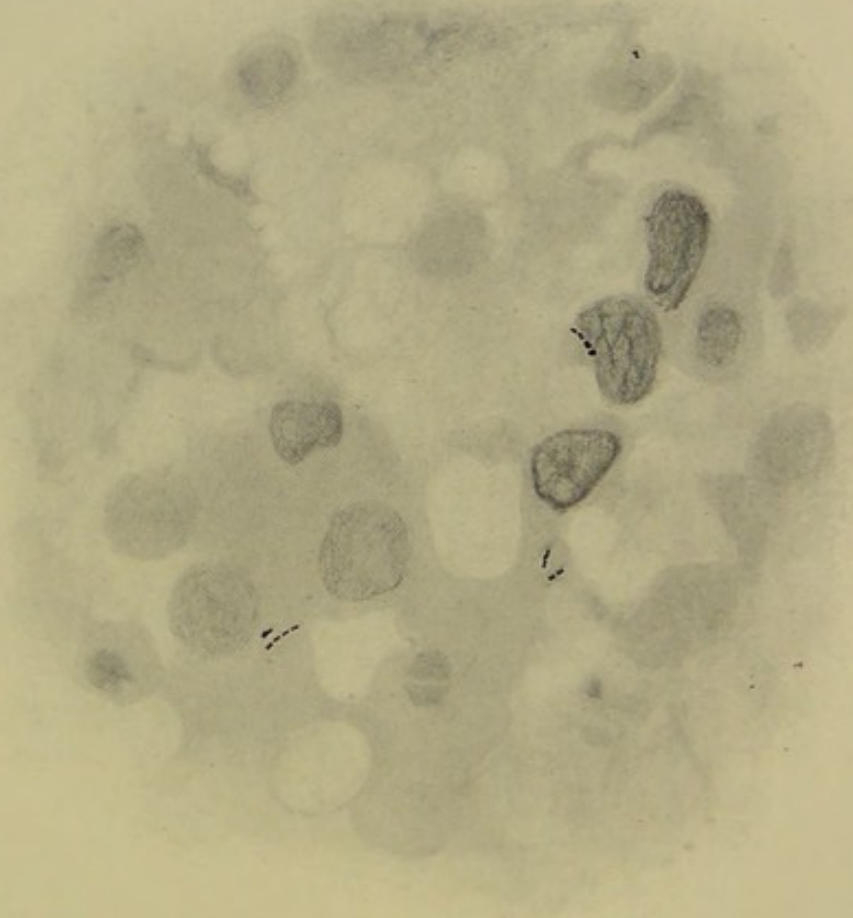


FIG. 78

Cerebro-spinal meningitis in rheumatic fever. Film from the cerebro-spinal fluid showing diplococci. (Zeiss, obj. $\frac{1}{12}$, oc. 12.)

when all believed the boy was quite convalescent. There are, however, other cases on record in which the supervention of cerebral rheumatism has been recorded during convalescence, and it is well known that this condition may occur when the first symptoms of rheumatism are slight as well as when they are severe. The most probable diagnosis thus appeared to be cerebral rheumatism.

The necropsy was made 15 hours after death. No changes were found in the affected joints. There was a slight excess of clear fluid in the pericardium and the mitral valve showed early endocarditis in the process of healing. There was also slight pleuro-pericarditis on the left side which was of recent origin. These morbid changes, we would point out, were entirely in accord with the occurrence of an attack of recent acute rheumatism. In no part of the body could any focus of suppuration be seen. Examination of the brain showed a condition of meningitis almost entirely basal in distribution and not suppurative. Except that it is spread further than is usually the case in post-basic meningitis, the appearance was almost identical with that condition. A good deal of turbid fluid was present together with flakes of exudation over the medulla, pons, and cerebellum. There was also a general spinal meningitis. The films showed minute diplococci in numbers. And we would point out that even in this extraordinary and virulent case it was by no means easy to find the micrococci in the pial tissues.

Cultures were taken from the blood in the heart, the pericardial and cerebro-spinal fluids, and brain. The cultures from the cerebro-spinal fluid contained a pure growth of a diplococcus in bouillon milk and glycerine agar. The virulence of these cultures was higher than is usually the case with the diplococcus and two rabbits inoculated with large doses died comatose within 24 hours. The blood film showed a minute diplococcus which was capsulated. The diplococcus was isolated from the blood of one and a small dose was injected intravenously into a third rabbit. After showing some loss of health this animal recovered. Return was made to the original culture and again a large dose produced rapid death, but a small dose was recovered from. *After two months interval* a large dose was again used, with the result that the rabbit developed arthritis of the shoulder joints and was killed in the

convalescent stage. The diplococcus was recovered from the damaged joints.

This case was clinically and experimentally very exceptional and we have only brought it forward as a contribution to the subject of meningitis in the rheumatic. Had our paper been brought forward in its original form we should have discussed the various explanations of the case and the details of its bacteriology, but to do so now would be out of place. We bring it forward, however, because we are inclined to the belief that it was a true rheumatic meningitis in spite of the fact that we observed capsulation of the diplococci in the rabbit's blood, which we admit has hitherto been regarded as a distinguishing feature of the pneumococcus. In any case it is worthy of record should others happen upon such a remarkable condition. Lastly, if for the moment this case is accepted as a true rheumatic meningitis the question arises as to how we are to link together these three remarkable rheumatic lesions of the brain termed (1) rheumatic chorea; (2) rheumatic hyperpyrexia or cerebral rheumatism; and (3) rheumatic meningitis. In rheumatic hyperpyrexia the rule is that no gross macroscopical lesion is found. Of this we believe there is no doubt, for we have referred to a number of such cases since the time of Fuller and have again and again found the same record of an absence of gross lesions. Nevertheless, recent research has shown that there are very grave microscopical changes. Thus Josué and Salomon [30] in 1903 found in such a case diplococci in the pia mater and in some of the cerebral blood capillaries, and demonstrated by Nissl's method profound changes in the nerve cells of the frontal and motor cortex. In October of this year Gandy and Borgnait Legneule [31] in a rapidly fatal case found diffuse chromatolysis. To us, then, it appears that this nervous lesion is an acute rheumatic toxæmia in contrast to the multiple and slight local lesions we believe exist in chorea. Rheumatic meningitis we would place between these two lesions, because there is on the one hand profound poisoning and on the other a severe local lesion. Are these nervous lesions, it may be asked, in any way comparable to rheumatic lesions of other organs? We believe so, and would venture the following comparison:

Mild rheumatic carditis and chorea.

Severe rheumatic pericarditis and rheumatic meningitis.

Acute fatal rheumatic cardiac dilatation and acute fatal rheumatic hyperpyrexia.

REFERENCES

[1] A paper read before the Neurological Society of the United Kingdom on November 23, 1905.

[2] The *Lancet*, September 22 and 29, 1900.

[3] Klebs, *Archiv für Experimentelle Pathologie*, 1875, Band IV, p. 469. Wilson, *Edinburgh Medical Journal*, 1885, vol. xxx, p. 1105. Mantle, "The Etiology of Rheumatism from a Bacterial Point of View," *Brit. Med. Jour.*, 1887. Popoff, *Meditz Prebavlena k'Morskomu Sbomekie*, 1887, p. 461. Von Leyden, *Congress der Innere Medicin*, Berlin, July 2, 1894. Triboulet and Coyon, *Comptes Rendus de la Société de Biologie*, 1898, p. 214. Westphal, Wassermann, and Malkoff, *Berliner Klinische Wochenschrift*, 1899, No. 29, &c.

[4] Poynton and Paine, *Transactions of the Royal Medical and Chirurgical Society*, 1902.

[5] *Transactions of the Fourteenth International Congress of Medicine, Section of Medicine*, 1903.

[6] Vernon Shaw, *Journal of Pathology and Bacteriology*, December 1903.

[7] Ainley Walker, *Practitioner*, 1903.

[8] Beattie, *Brit. Med. Jour.*, December 1904.

[9] Loc. cit. [10] Loc. cit. [11] Loc. cit.

[12] Predtetschensky, *Vratch*, 1901, No. 24.

[13] Fritz Meyer, *Deutsche Medicinische Wochenschrift*, 1901.

[14] Singer, *Verhandlungen des Congresses für Innere Medicin*, 1897, 1899.

[15] Allaria, *Rivista Critica de Clinica Medica*, 1901, No. 47.

[16] Jarvis, *Thèse de Paris*, 1902.

[17] Cole, *Journal of Infectious Diseases*, vol. i, No. 4, 1904.

[18] Longcope, *American Journal of the Medical Sciences*, 1904.

[19] Herry, *La Semaine Médicale*, October 4, 1905.

[20] Philipp, *Deutsches Archiv für Klinische Medicin*, Band LXX, Hefte 1–3.

[21] Walker and Ryffel, *Brit. Med. Jour.*, September 19, 1903.

[22] Gordon, *Lancet*, November 11, 1905, p. 1400.

[23] Dana, *American Journal of the Medical Sciences*, 1894, p. 31.

[24] Apert, *Société de Biologie*, January 20, 1898.

[25] Poynton and Paine, *Transactions of the Fourteenth International Congress of Medicine, Section of Pediatrics*, 1903.

[26] Poynton and Shaw, *Transactions of the Pathological Society*, 1904.

[27] Reichart, *Deutsches Archiv für Klinische Medicin*, 1902, p. 504.

[28] Poynton and Paine, *Transactions of the Pathological Society*, 1901.

[29] Poynton and Paine, "Some Further Investigations upon Rheumatic Fever," *Lancet*, May 4, 1901, p. 1260.

[30] Josué and Salomon at a meeting of the Paris Hospitals Medical Society, July 25, 1905.

[31] Gandy and Borgnait Legneule at a meeting of the Hospitals Medical Society, Paris, October 27, 1905.

PAPER NO. XIX

A CONTRIBUTION TO THE PATHOLOGY OF CHOREA

By Dr. F. J. POYNTON and Dr. W. GORDON HOLMES

(Reprinted from the *Lancet*, October 13, 1906.)

The collaboration of Dr. Gordon Holmes, then Director of the Nervous Disease Research Fund at the National Hospital for the Paralysed and Epileptic, enabled us in this paper to study the minute pathology of chorea by the most recent methods of that date. The number of cases of fatal chorea that were investigated was increased and a detailed explanation of the occurrence of rheumatic chorea given in the light of the changes that were found in the nervous system. In addition, a study of a case of chorea occurring in pregnancy enabled us to discuss the nature of this condition, which, in accord with the experience of other investigators, we believed to be frequently rheumatic in nature.

In the present communication we are, firstly, adding three more to the recorded observations of the presence of a diplococcus in the pia mater of cases that have proved fatal while suffering from chorea. In addition, this micro-organism has been demonstrated in the brains of these cases lying in the perivascular spaces and connective tissue. Secondly, we have also studied by the most recent methods the two series of changes—viz., those affecting the connective and vascular tissues and those which occur in the nervous tissues in chorea. And, lastly, we have demonstrated that in a case of chorea which occurred in a first pregnancy lesions were present similar to those that were found in the rheumatic cases. Such opportunities could never have offered themselves if it had not been for the kindness of Sir Cooper Perry and Dr. H. S. French, Dr. J. Rose Bradford and Dr. H. Batty Shaw, and we are greatly indebted to them for the pathological material and permission to use the clinical and post-mortem notes of these cases. Deaths from chorea are so rare that the opportunities

for testing the results in several cases at short intervals are most exceptional, but through their kindness these three cases came to us within a month and gave us an opportunity of repeating and comparing our observations.

The Clinical Cases

CASE 1. Our first case, for which we are indebted to Dr. Shaw, was that of a girl aged seven years, who was admitted to the Children's ward at University College Hospital on March 25, 1906. Her illness had commenced three weeks previously with multiple arthritis, ushered in with acute malaise and vomiting. After a temporary improvement chorea and pericarditis developed, and when admitted her condition was hopeless. Death occurred two days later from heart failure, the chorea having lasted about 17 days. While under observation the temperature ranged between 104° and 99° F., the chorea was very severe, the pericarditis was general, and valvular disease was also present. In her previous history there was a record of an attack of rheumatic fever at five years of age. The post-mortem examination showed general and recent pericarditis, bilateral pleurisy, mitral endocarditis, and myocarditis.

This case was one of extreme severity and illustrates a difficulty that has to be reckoned with in studying chorea. During the last week of life blebs full of serous fluid developed upon the back and elsewhere and the incessant movements rapidly converted them into open sores. An occurrence such as this must, we readily admit, introduce the question of secondary infection and increase the difficulties of an accurate interpretation of any results. For our own part we are sceptical that, under these conditions, a secondary infection will explain the results of post-mortem investigation, because it has been repeatedly demonstrated that in acute rheumatism similar bacteriological results to those we obtained on this occasion can be shown when there is no question at all of open sores.

There is yet another point of interest about this case. Some eminent bacteriologists dispute any direct association between the diplococcus and acute rheumatism and some have failed to find the micrococcus after repeated search in cases of rheumatism. In this case, however, a pure growth

of a diplococcus was obtained from the heart's blood by Dr. F. H. Thiele, clinical pathologist to University College Hospital. Its presence was demonstrated in the pericardium by Dr. T. Lewis, the house physician to the case. It was again demonstrated by one of us in the pia mater and by another in the brain, and was cultivated by Dr. Paine, and on experimental injection into animals produced multiple arthritis and pericarditis of the usual type. It will be seen, then, that five different observers independently recognised the occurrence of a diplococcus in this case, which had the features of the diplococcus described in rheumatism.

Pathological investigation. Only the right half of the brain, brain-stem, and cerebellum and a portion of the diseased heart valve were received for examination. *Macroscopical examination.* The vessels of the meninges and cortex of the hemisphere, and to a less extent those of the membranes on the base of the brain and brain-stem, were very much engorged. No exudation or signs of inflammation were visible to the naked eye, but several small subpial hæmorrhages could be seen on the convexity of the hemisphere. *Microscopical examination.* Sections stained with hæmatoxylin revealed great congestion of the blood-vessels of the membranes and of the brain itself, and in many places small hæmorrhages were visible, especially on the under surface of the pia mater. A small proportion of the vessels of the pia-arachnoid, generally the smaller arteries, were thrombosed, especially over the convexity of the hemisphere, and there was in places definite evidence of serous exudation and small round cell infiltration into the membranes in the immediate neighbourhood of the vessels. Thrombosed vessels were still more common in the cortex and subcortical white matter, but in the majority the clots seemed to be quite recent, though some were partially organised. Thrombosed vessels could be occasionally followed into, or found within, small patches of softening, which lay most frequently in the deeper layers of the cortex. The destruction of tissue within them was never complete; there was considerable serous exudation into the recent ones, while the older were marked by proliferation of neuroglial nuclei and sclerosis. There was also small round cell infiltration into the sheaths and perivascular spaces of many of the vessels which were not thrombosed and a polymorphonuclear leucocyte was occasionally seen

among them. These changes were equally marked over the whole hemisphere and within the basal ganglia, but no foci of necrosis were observed in the cerebellum, pons, or medulla, though here, too, there was considerable congestion of the vessels and frequently small round cell infiltration into their sheaths.

When the brain was examined by Nissl's method definite cell changes were found, which were greater in the cerebral cortex than in any other part of the central nervous system. Practically all the cortical cells were affected ; as a rule they were swollen and distended, their tigroid had partly disappeared so that they stained diffusely or occasionally almost uniformly, and their nuclei, which were swollen and excentrically situated in a certain number of the cells, stained more deeply than normal. The nucleoli appeared unaltered and the cell processes seemed normal except that they were not easily visible owing to diminution of their chromatophilic substance. The degree of affection of the large Betz cells was very variable. In the majority there was only slight chromatolysis immediately around the nucleus where the Nissl bodies were broken up into a deeply staining granular material, while they remained normal in the periphery of the cell and in the dendrites. In the next stage there was more extensive perinuclear chromatolysis and the nuclei were more generally swollen and more frequently excentric. A small number of cells were still more severely affected ; their outlines were scarcely recognisable, their nuclei were shrunken and deformed, and no stainable substance was visible in them. The cells of the basal ganglia were less affected ; there was at the most only evidence of commencing chromatolysis and slight swelling of the nuclei. The cells of the different portions of the brain-stem were in much the same state ; they stained rather faintly and there was commencing disintegration of their tigroid masses. No definite changes were recognised in the cells of the cerebellum. Various portions of the forebrain and brain-stem were treated by Marchi's method. A few degenerated fibres were found on the borders and neighbourhood of the small patches of softening, but there was otherwise no evidence of disease in the cortex except in the presence of dark granular masses in the perivascular spaces or in the walls of the blood-vessels, which probably represented the process of removal of some degenerate products.

Bacteriological examination. Thin films of pia mater were stripped off the brain, fixed on slides, and hardened in alcohol. They were then stained by Löffler's methylene blue and examined under an oil-immersion lens. In other places the pia mater was cut along with the brain it covered in paraffin and stained by the same method. On careful search bacteria were found in the pia mater; the majority appeared as isolated diplococci of small size, but frequently larger groups of micrococci, many of which lay in pairs, were visible, and occasionally a single micrococcus was also seen. The morphological characters of the micrococci were in every place the same; they were remarkably small on the whole but rather irregular in size. No other bacteria were found in the meninges. Similar diplococci were found in sections of the brain which had been cut in paraffin and stained in the same way. They were seen, however, only in the loose connective tissue surrounding the vessels and in the perivascular spaces; despite careful search none were discovered in the brain tissue. Their presence did not seem to bear any relation to the intensity of the vascular changes or to the presence of thrombosis, but infiltration by small round cells, evidently of vascular origin, was generally visible in their neighbourhood both in the meninges and in the brain. Groups of similar micrococci were found in the ulcerated heart valve. Here they generally lay in groups in which the diplococcic arrangement was readily visible, most frequently at the junction of the necrotic and inflammatory tissue, but in places they extended to the surface of the ulcers or vegetations. Similar diplococci were present in the inflammatory tissue in the pericardium. Morphologically these micrococci seemed identical with those found in the meninges. Dr. Paine kindly investigated for us the cultures obtained by Dr. Thiele from the blood in the left ventricle and found that intravenous injection into the auricular veins of rabbits produced arthritis and pericarditis.

Case 2. The second case, a boy aged 14 years, was admitted to University College Hospital, under the care of Dr. Bradford, on May 8, 1906. He had been ill for two months and in his past history there was a record of several attacks of subacute rheumatism. The first symptoms of the present illness began with pains all over the body, and for some weeks before admission he had developed præcordial

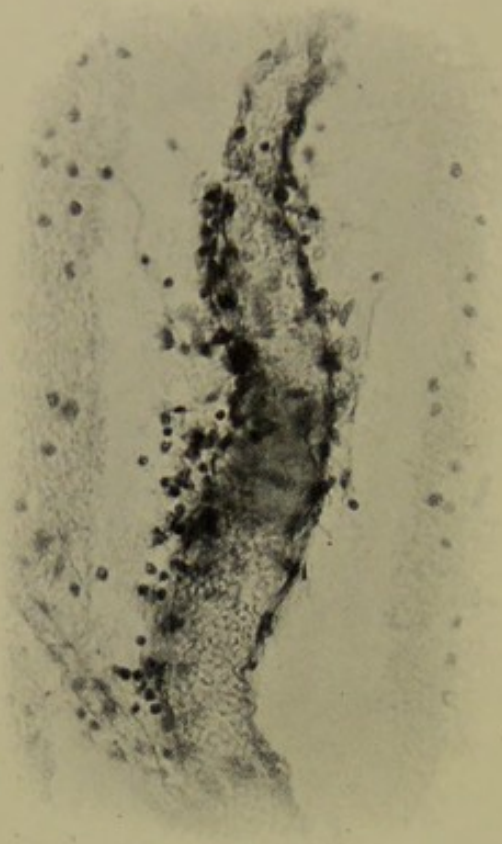


FIG. 79

Human chorea. Reproduction of a microphotograph showing small round-cell infiltration into the sheath and perivascular space of a vessel in the subcortical white matter.

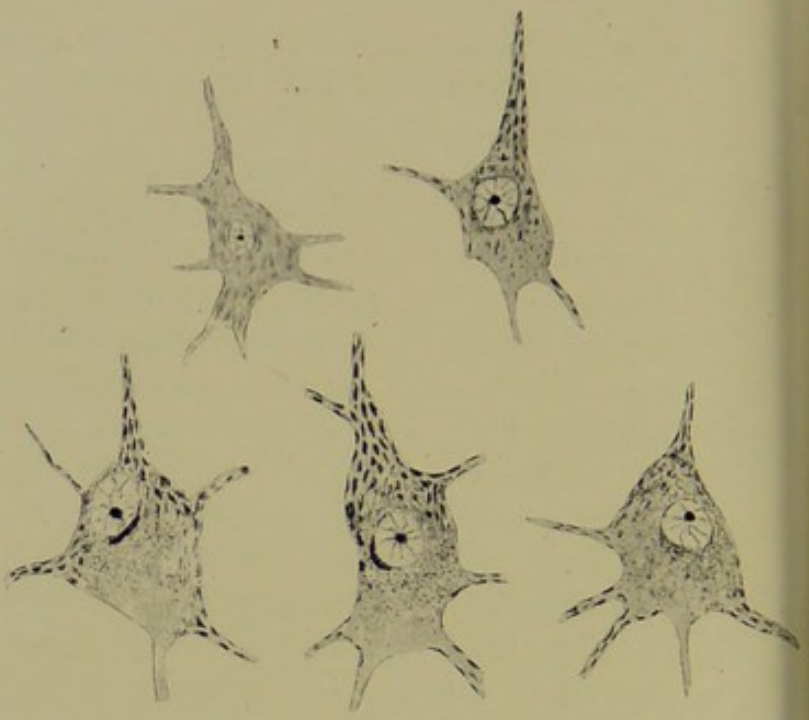


FIG. 80

Two large pyramidal cells and three Betz cells from the precentral convolution of Case 1. Showing various degrees of chromatolysis.

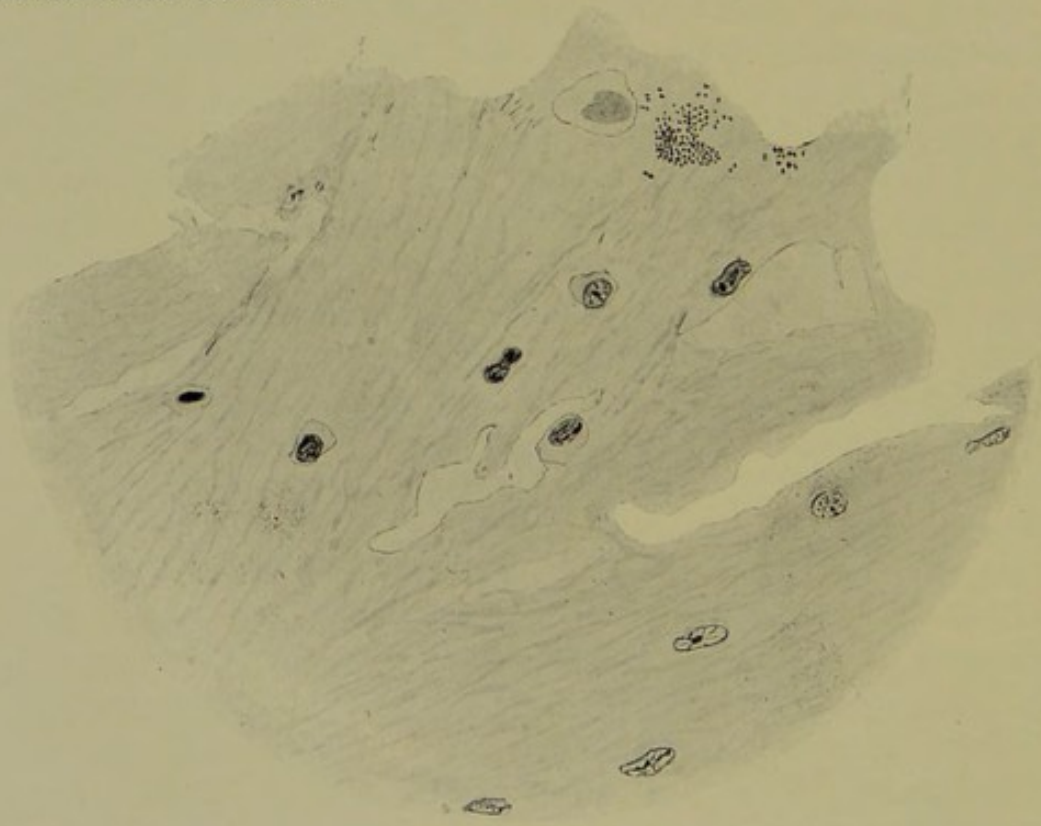


FIG. 81

Human chorea. Section of a vegetation on the mitral valve showing the presence of diplococci (Case 3.)

pain, cough, and dyspnœa. His condition was critical. On admission the temperature was 102° F., the pulse-rate was 120, and the respiration was 28 to the minute. The heart was rapid and excited, with a loud apical systolic murmur. There were crepitations at the bases of both lungs and the mental state was dull. After he had been a few days in the hospital the excited action of the heart suggested pericarditis in spite of the fact that there was no pericardial friction. In addition, patches of penumonia had now developed. On the 13th the boy was actively delirious and chorea commenced and rapidly became violent. Death occurred on the nineteenth day, the temperature to the end never becoming hyperpyrexial. *This case is of exceptional value because the chorea developed under observation.*

The necropsy showed that there was recent pericarditis over the posterior surface of the heart. The pericardium was adherent over the front and there was recent endocarditis of the mitral and tricuspid valves. The lungs were in a condition of acute œdema.

Pathological investigation. Only the brain and brain-stem were received. Examination revealed a condition so similar to that of Case 1 that but little additional description is needed. *Macroscopical examination.* To the naked eye the state of the brain was identical with that of Case 1. There was a similar engorgement of the vessels with subpial hæmorrhages. *Microscopical examination.* As in the previous case, the engorgement of the vessels was a very prominent feature in sections of the membranes and brain. Very few of the vessels were, however, thrombosed and only two small and incomplete patches of softening were found though a large number of sections were examined. Many of the vessels contained large masses of leucocytes and there was in places considerable œdema in the perivascular spaces and the brain tissue around them. In this case, on the other hand, there was more cellular infiltration into the meninges and into the sheaths and perivascular spaces of the cerebral vessels. The use of Nissl's method revealed similar changes in the nerve cells, greatest in the cortex, and approximately equal in all its regions. In this case, too, the nerve cells of the basal ganglia and brain-stem were less affected than the cortical cells. No degenerated medullated fibres were made visible by Marchi's

method, but irregular masses, which stained dark by osmic acid, similar to those in Case 1, were found in the perivascular spaces of the brain.

Bacteriological examination. The examination was conducted in the same way as in Case 1 and yielded similar results. The diplococci were, however, more numerous in the meninges of this case and groups of similar micrococci were easily found in the adventitial sheaths and perivascular spaces of the brain. Neither the heart valves nor pericardium were received for examination.

CASE 3. For the third case we are indebted to the kindness of Sir Cooper Perry and Dr. French. This was a case of chorea occurring in a first pregnancy without a previous history of chorea or rheumatism. It is clear that the interpretation of any of the results that we have obtained in this case must be made with minds alive to possible fallacies. We shall on this account plainly state that the results are put on record as facts observed in a single case only and the interpretation put upon these facts is left open to free criticism. The history of the case was published by Dr. French and Mr. H. T. Hicks [1] and is as follows.

"R. D., aged 21, had been married four months and was pregnant at the second month for the first time.

"*History.* She had had no previous chorea nor acute rheumatism. The present chorea began at the second week of pregnancy. The movements were slight at first and got worse gradually. On admission she was so violent and noisy that she had to be taken to the strong room. Nasal feeding was resorted to, the choreic movements being controlled by chloroform. She was emaciated. There was no bruit.

"*Result.* The uterus was evacuated after rapid dilatation under chloroform; the patient seemed quieter next day. The chorea ceased but the patient became collapsed and died on the fifth day after the uterus was emptied.

"*Autopsy.* There were recent vegetations all along the mitral valve; there were no infarcts. Cultivations of the heart blood showed bacillus coli communis only. Cultivations from the spleen remained sterile after incubation for three days at 37° C."

A most interesting feature in this case, which, as we have just pointed out, gave no personal history of rheumatism,

was the condition of the mitral valve. This valve showed a row of early vegetations which were indistinguishable from those on the valve in Case 1, which was the result of an obvious and exceedingly active attack of acute rheumatism. These two valves were sent to us in the same week, and their resemblance was most striking ; nor did the resemblance cease here, for on section we found that the valve from the case in which there was no personal history of rheumatism and the valve from the active rheumatism *both contained diplococci similar in appearance and distribution, and both showed tissue changes of similar nature.*

Pathological investigation. Only the brain and brain-stem and portions of the ulcerated cardiac valves were obtained. *Macroscopical examination.* To the naked eye the brain was similar to that of the other two cases, but there was less vascular engorgement. *Microscopical examination.* Vascular engorgement of the brain and its membranes was also a prominent feature in this case, but only very few thrombosed vessels could be found and in all these the clots appeared to be quite recent. None were fully organised and there were no such changes in their intima as would have resulted from long occlusion. No definite patches of softening were found, though around some of the thrombosed vessels the brain tissue was slightly necrotic and infiltrated by serum. There was also here less small round cell infiltration into the walls and perivascular spaces of the cerebral vessels, though in places it was quite marked.

While the changes in the vascular system were less in degree, though similar in kind, in this case than in the two above described, the affection in the nerve cells was considerably greater. In scarcely one of the cortical cells was tigroid visible in the form of ordinary Nissl bodies ; the protoplasm stained diffusely or almost uniformly and generally darker than normal. The nuclei were definitely enlarged, especially those of the large pyramidal cells and the Betz cells, but the nuclear chromatin remained as a rule easily visible in a pale ground and apparently unaltered. In other cells, however, the nuclei retained so much stain as to make them appear dark and almost homogeneous ; these nuclei were often smaller than normal and occasionally irregular in shape. In some cells, especially in the Betz cells, the nuclei were excentric, but in the majority they remained central. No pathological

changes were observed in the nucleoli. Some of the affected cells, especially the larger ones, were considerably shrunken. These changes were equally marked in all parts of the cerebral cortex. The cells of the corpus striatum and of the thalamus were practically identically affected; no absolutely normal cell was found in them. Some were considerably swollen and all stained so diffusely that no clumps of tigroid could be distinguished either within them or their dendrites. The cell changes were less pronounced in the pons and medulla; the cells of the motor nuclei had undergone relatively slight tigrolysis and had merely a punctate appearance, due to fragmentation and partial absorption of the Nissl bodies. None of them were swollen and their nuclei were as a rule normal. The cells of the sensory nuclei and of the rest of the grey matter of the pons and medulla were somewhat similarly affected. The Purkinje cells of the cerebellum were only very slightly affected, but those of the nucleus dentatus had suffered more severely; they were swollen, their nuclei often lay excentric, and in the majority there was complete disappearance of the Nissl bodies. No degenerated fibres were found on examination by Marchi's method, but many of the medullated fibres of the forebrain were coloured a faint brownish tint, probably representing a slight chemical change in the myeline. The same evidence of degeneration products was visible in the perivascular spaces and vessel walls as in the other two cases.

Bacteriological examination. Micrococci, generally lying as diplococci and identical in appearance with those described in Cases 1 and 2, were found after careful searching in the pia mater of the forebrain and in the walls of the cerebral vessels. They were infrequent in the portions of tissue examined, but quite as numerous as in Case 1. Similar diplococci were also found in the diseased heart valve, in the same position as in Case 1.

Part III.—The Pathology of Chorea

It now remains to interpret the results that were obtained in these three cases: firstly, in their bearing upon the nature of chorea; and, secondly, with reference to the relationship of chorea and rheumatism.

I. *The nature of chorea.* In considering the changes described as the anatomical substratum of chorea we are

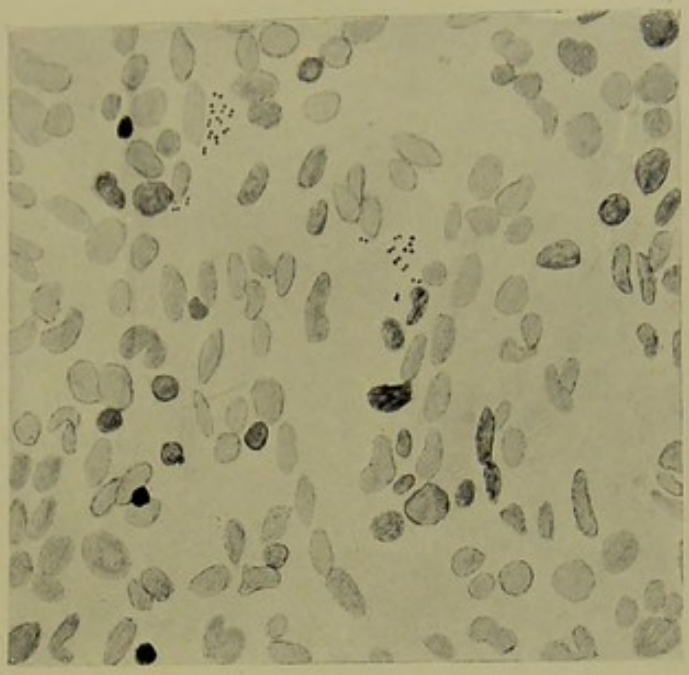


FIG. 82

Human chorea. Film of the pia mater showing the presence of two groups of diplococci.

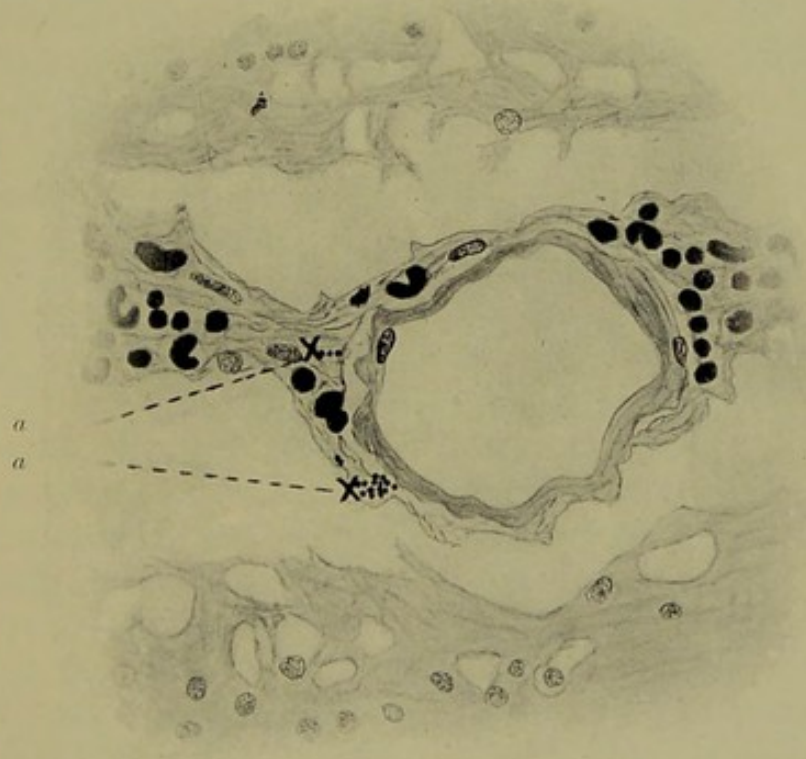


FIG. 83

Human chorea. Section of cerebral cortex showing (*a*) the presence of diplococci in, and cell infiltration of, the adventitial sheath of a vessel.

unhappily limited by the fact that in none of the three cases was the spinal cord obtained for examination. Yet this restriction is not serious, for though definite pathological changes would probably have been found there, as in every other part of the central nervous system, it would be impossible to assume that the cord played any great part in the production of the choreal movements. For, quite apart from the distribution of the movements, their nature makes it highly improbable that they arise in the spinal cord. To quote Dr. J. Hughlings Jackson, "these movements are not mere spasms and cramps, but an aimless profusion of movements, of considerable complexity, much nearer the purposive movements of health," [2] and therefore "it is certain that the part diseased serves in highly special and complex coordinations, and that thus it is a part very high up in the nervous system." [3]

The study of the central nervous system has shown that the pathological changes which form the morbid anatomy of the disease are composed of (1) vascular and inflammatory changes in the central nervous system and its membranes; and (2) changes in the nervous tissue itself, consisting of destructive lesions secondary to the vascular changes and of alterations in the morphological characters of the nerve cells.

The most prominent vascular change in all three cases was the great hyperæmia of all parts of the brain and the presence of thrombosed vessels; the latter were rather numerous in Case 1 but more rarely seen in Cases 2 and 3. Whether the thrombi were primary or secondary to embolism is impossible to say, but no emboli were seen in the sections which were studied. In Case 1 patches of softening were found associated with, and evidently a result of, these vascular occlusions, but they were very infrequent and rarely pronounced in degree in Cases 2 and 3. But more constant in all three cases was the evidence of inflammatory reaction shown by the presence of perivascular small round cell infiltration and serous exudation around the vessels. The consideration of these changes is interesting in relation to the theory of Kirkes, which was supported by Hughlings Jackson [4] and Broadbent,; that they are the ætiological factors of the choreal movements. According to Dr. Hughlings Jackson it is apparent that the disorder of function must arise from instability and overaction of the

nerve tissue, which he explains by the increase of nutrition due to the collateral hyperæmia that results from vascular occlusion by embolism, assuming, of course, that only the smallest vessels are occluded. Ingenious though this theory is, it is hardly acceptable on the evidences afforded by the investigation of our three cases, for though hyperæmia was very pronounced there was, in two of the cases at least, very little evidence of embolism on microscopical examination. It seems to us that there is a more definite reason for the congestion of the vessels which we shall consider below. Further, in view of the pronounced cell changes and the presence of micro-organisms in the brain and its membranes, other possible factors must be considered. The foci of necrosis, we would add, may be neglected in seeking the causal agent, as they are purely destructive lesions and cannot, therefore, *directly* produce active or positive symptoms.

As the nerve cells of one or several regions must be the direct agent in production of the movements the changes found in them are important and claim our first consideration. At first the question arises, What is the significance of these changes ? Under what conditions are they known to develop ? The changes are those described by the term chromatolysis ; they consist of partial solution of the stainable substance of the cell and slight alteration in the appearance or even position of the cell nucleus ; in some of the cortical cells, especially in Case 3, the changes had advanced further, and both the bodies and nuclei of the cells stained deeply and homogeneously as though they had undergone coagulation necrosis. These changes represent a vital reaction of the cell to some abnormal influence. It is known that chromatolysis is found in cells which have been subjected to overwork, but the possibility of over-activity being the cause in these cases may be at once rejected, for the cell changes were universal throughout the brain and brain-stem, that is, they occurred in some groups of cells which it is groundless to assume were over-active. In the cells of the motor area, however, and especially in the Betz cells, over-activity may have had a part in the pathogenesis of the changes. They were certainly not the result of pyrexia, for the pyrexia in these cases was not considerable, with the exception of the last few days of life in the case of chorea of pregnancy.

The assumption that the changes described are due to the action of bacterial toxins, on the other hand, is suggested by the frequent association of chorea with the undoubtedly infective condition known as rheumatism, and by the discovery of micro-organisms in the central nervous and vascular systems, both by ourselves and other workers. This view is compatible with the results of examination of the nerve cells in other infective diseases—*e.g.*, diphtheria, typhoid fever, and septicæmia, where analogous changes have been found (Babes, Marinesco, and others). The assumption of a bacterial toxin (whether specific or not matters not) explains also the local vascular disturbances, which may be regarded as a reaction to its presence, the occurrence of degeneration products in the walls of the vessels and the evidence of the slight chemical change revealed by Marchi's method in the medullated fibres of Case 3.

If it is accepted that the action of a toxin is the immediate agent in the causation of choreal movements the question then naturally arises, if chorea is cerebral rheumatism in the sense that it is produced by the same bacterial poisons which give rise to the symptoms of ordinary acute rheumatism, is it necessary that there should be infection of the brain and its membranes by the bacteria, or is it sufficient that the toxins should be carried by the blood and lymph from some other seat of manufacture? It does not seem possible to give an absolute answer to this question, though the presence of bacteria in the brains of the three cases we have examined suggests that its affection depends on the direct invasion of it by the bacteria. The occurrence of hemichorea also makes a local infection probable, as unilateral symptoms can be scarcely attributed to a general infection; it is also supported by the previous demonstration of the diplococcus rheumaticus in all the other important lesions it produces. On the other hand, it must be borne in mind that it has been shown by Laignel-Lavastine that similar changes in the brain cells may be the result of tuberculous toxæmia without bacterial infection of the brain, and Babes and others have found similar cell changes after the experimental injection of toxins alone. The examination of a series of brains from cases of acute rheumatism without cerebral symptoms will be necessary to decide this point.

It now remains to attempt an explanation of the production of chorea by these toxins, whether produced locally or circulating in the blood and lymph. Here we have to deal with the little-understood physiology of the nerve cell and our arguments are consequently more or less limited to analogy. Thus, it is well known that symptoms of instability and over-action of the nerve cells, analogous, if not similar, to those of chorea, may result from the action of the toxin of tetanus and that similar excess of movement is produced by strychnine. Nor does the possible analogy end here. The excess of activity produced by strychnine, and perhaps, too, by tetanus, may be followed by paralysis of the concerned movements, presumably due to exhaustion of the nervous centres, and it is possible that some of the choreal palsy may be due to a similar exhaustion of the active centres, although it seems to us more probable that the palsy of movement so frequently seen in chorea is a direct effect of toxic action. It is conceivable that the same toxin which produces symptoms of excitation may, when acting in greater concentration or more rapidly, paralyse the functions of the cells. Such a reversal of action is seen on the administration of morphine or chloroform ; small doses acting for a short time produce excitation, while in larger amount they annul the functions of the previously excited centres. This toxin, though probably specific in the sense that it is constantly the product of a single variety of bacteria, has certainly no special action on any part of the central nervous system in the sense that it affects these and spares the others, for both the vascular and nerve cell changes were found in every region of the brain and brain-stem. The explanation of the predominant affection of the motor system in chorea is probably that its symptoms are always the most apparent and that it is the system which reacts most easily to excitation. But chorea is not composed of one symptom alone, there may be in addition positive or negative symptoms of speech, sensation, and even of the highest psychical state. The anatomical basis of such disturbances of function is represented by the changes described in the nerve cells in the different parts of the brain.

The aim of this paper is such that it is not necessary to commit ourselves to a definite expression of opinion as to the disturbance of what portion of the nervous system yields the

predominant symptom of chorea. It has been assumed, though often only tacitly, by the majority of authors that the higher motor centres are concerned and it has therefore been placed in the cerebral cortex, or, in the prelocalisation days, in the corpus striatum. As Dr. Hughlings Jackson has so clearly shown, the nature and distribution of the movements, as well as the general physiology of the disease, confirm this view, but the pathological changes are so general and widespread throughout the whole central nervous system that they can neither support nor contradict any theory of localisation.

II. *Chorea and Rheumatism.* We are thus led by this study to the conclusion that the causation of chorea is to be found in the action of bacterial poisons on the brain. Further, the available evidence points to the occurrence of a local infection to which the widespread changes in the nervous system are due. Finally, we believe that this infection is of a rheumatic nature ; it is, then, necessary to see how far it is possible to correlate this conclusion with the association of chorea and rheumatism.

The first point in this consideration is the frequency of the association of chorea and rheumatic fever. This is explained by looking upon chorea in the rheumatic as a symptom of rheumatic infection and by regarding the " diplococcus rheumaticus " as the cause. This, too, explains the clinical truth that chorea may be the first evidence of acute rheumatism or be one of many coincident manifestations or be a late episode of the disease. Which of these events may happen will depend upon the date at which the cerebral infection occurs. If we accept the undoubted fact that chorea may be the first symptom of acute rheumatism we are at once confronted with the question whether or not chorea is only a manifestation of acute rheumatism. It will be a distinct advance in our knowledge when the answer to this is finally settled. The difficulty is apparent and turns upon the doubt as to whether such movements and such cerebral disturbance as we see in chorea can be produced by more than one agent. At the present time there is evidence upon both sides but the bulk of it strongly favours the view that chorea is mostly rheumatic and that when chorea occurs without any history of rheumatism it is presumably the primary rheumatic symptom and in practical medicine is best looked upon as a stamp of rheumatism.

The tendency for chorea to relapse or to occur several times in the life of an individual is explained in precisely the same way as the relapses and recurrences of rheumatic heart disease and arthritis ; that is to say, either there is a fresh outburst of a slumbering infection or a fresh infection has occurred. The onset of chorea is not unlike the onset of the other rheumatic manifestations, for, as with these, it may be gradual, subacute or acute. If the infection is slow in making itself felt, and yet eventually succeeds, then the course of the chorea is slow. The acute cases, on the other hand, recover more rapidly. Should chorea arise while the patient is under observation this sequence of events is observed whatever method of treatment is adopted, the stage of onset, the stage of the developed disease, and, lastly, the stage of retrogression. This is the course that we notice in all infections that cannot be cut short by some specific remedy.

When chorea follows acute arthritic or cardiac rheumatism the cerebral infection may date from the original one, and have remained latent for some time, for there is no doubt that chorea may smoulder on for weeks without distinctly declaring itself. In other cases an entirely new infection may have occurred, which this time has attacked the brain. Lastly, the cerebral infection may be metastatic, in the sense that it has arisen after the original attack of acute rheumatism by a metastasis from a focus of infection elsewhere, which itself was the result of the original attack ; this focus may be situated, for instance, in the heart or in the joints. As Vernon Shaw has demonstrated in animals, a primary focus in a joint, produced by a local injection of the diplococcus, may be followed by the appearance of pericarditis. Chorea is thus very reasonably explained both as the first symptom and the last of acute rheumatism, and when it occurs simultaneously with arthritis and endocarditis it is clearly part of a widespread infection. The complete recovery that so frequently occurs in chorea is not infrequently brought forward as an argument against its rheumatic origin. It is, however, clear that acute rheumatism is a disease to which there is great resistance, for it is rarely fatal ; and it is also evident that the various tissues resist the poisons with different degrees of success. The heart often recovers partially but is usually maimed ; the joints often recover completely, pleurisy generally leaves adhesions,

but the subcutaneous nodules and cutaneous eruptions disappear. The renal inflammation, again, is usually transitory. Chorea is to be grouped among the more transitory of the rheumatic lesions, for although there is no doubt that some cases may last for many years the anatomical lesions are clearly recoverable as shown from the pathological changes in these cases.

At this point we would make passing allusions to the probability that even more delicate changes occur in the nervous system as the result of rheumatism. Clinical observers have pointed out that rheumatic children are singularly nervous and emotional and there is no doubt that a child's nature may be greatly changed by an attack of rheumatism, particularly if this should be of the cerebral type. To our knowledge parents have volunteered this statement where examination has shown that no cardiac lesion has been left behind and the attack of rheumatism has certainly subsided. It is possible that such psychical alterations are the result of organic changes of an even more delicate nature than those met with in chorea.

A difficulty which attends the complete explanation of other infective processes which affect the brain is equally present with chorea. We cannot say why in some cases the brain suffers and in others it does not. The well-known importance attached to fright in the ætiology of chorea has close bearing upon this difficulty, for overstrain of any system tends to lower its vitality and in the case of the nervous centres, whether that overstrain be abrupt, as in fright, or chronic, as in the strain of school-work or mental anxiety, the lowering of the vitality is a predisposing cause for the rheumatic infection to gain a foothold.

Part IV.—Chorea and Pregnancy

The third case in which chorea was associated with pregnancy raises two questions of importance. Firstly, whether this chorea is a rheumatic chorea intensified by the condition, and secondly, a far wider one concerned with the influence of pregnancy and the puerperal state upon the rheumatic infection. Chorea in pregnancy is probably a rheumatic chorea. We get support for this statement from the clinical observations

of others upon the association of rheumatism and chorea in pregnancy. Thus in a recent paper by Wall and Russell Andrews [6] Buist's statistics are quoted, who found that in 226 cases of chorea in pregnancy 45 gave a previous history of rheumatism and 66 a previous history of chorea. From their own observations they found that in 23 out of 37 cases of chorea in pregnancy there was a previous history of chorea and in 16 out of 37 a previous history of rheumatism. Still more recent and equally convincing evidence is furnished in a paper by Dr. Herbert S. French and Mr. H. T. Hicks.[7] Here 29 consecutive cases of chorea gravidarum were reviewed from the records of Guy's Hospital and in no fewer than 19 of these there was a previous history of rheumatism or chorea and 15 of these 19 had suffered from chorea before marriage. As a result of their investigations these authors add: "This is so large a proportion of the whole that we feel convinced that chorea gravidarum and infantile chorea have a similar pathology." This single case of ours strengthens the position to this extent, that it has enabled us to show the presence of a diplococcus in the nervous system and heart valves and to demonstrate that the morbid changes in the brain are essentially similar to those in rheumatic chorea. Further, the mother of the patient was at the same time in Guy's Hospital suffering from recurrent ascites due to heart disease. There are, then, the chorea, the condition of endocarditis of the mitral valve described above, and the nature of the mother's illness, which legitimately suggest that this woman was suffering from a rheumatic chorea. It will not be forgotten that in childhood chorea may be the only evidence of rheumatism, and it is difficult not to believe that when in a case of chorea we search for a history of rheumatism we may often be in the position of one searching for a history of tuberculosis in a patient suffering from tubercular meningitis. We are, in fact, looking for evidence of a disease with that evidence staring us in the face. It is also becoming increasingly apparent that the most frequent cause of chorea in pregnancy is, in all probability, a rheumatic infection. Two cases under the care of one of us are worth mention in this context. One of these while a child was a patient in the Hospital for Sick Children, Great Ormond-street, with chorea and rheumatic endocarditis. At the age of 16 years she became pregnant and was admitted

to University College Hospital suffering from chorea of terrible severity from which, after a very long and severe illness, she recovered. The other was a young woman who suffered from rheumatism with chorea as a girl, who passed through a first pregnancy without chorea and developed chorea 12 months later when she was not pregnant. Finally, it is recognised that induction of labour does not so influence the course of these cases of chorea that the pregnancy can be claimed to be more than a predisposing cause. All these points suggest that the chorea in pregnancy is of the same nature as the chorea of childhood.

The second and wider question of the influence of pregnancy and the puerperal state upon rheumatic infection needs prolonged investigation. We have, on the one hand, a great infective process, the rheumatic, and on the other, an important physiological process, which in some measure disturbs the entire metabolism of the individual. Chorea is more obstinate and dangerous in pregnancy, heart disease is liable to be more active, and arthritis more obstinate. Concerned with the same problem is the possibility that a puerperal fever may result from a rheumatic infection at the end of pregnancy and it is known that direct infection of the fœtus may occur.

Finally, we would point out that the conclusions from our paper in the first place support the clinical evidence that chorea is a manifestation of acute rheumatism ; and secondly, that the demonstration of diplococci in each of the three cases is a striking confirmation of the assertion that " the diplococcus rheumaticus " is the infective agent in acute rheumatism.

REFERENCES

[1] *Practitioner*, August 1906.
[2] *Edinburgh Medical Journal*, vol. xiv, 1868.
[3] *Medical Times and Gazette*, 1875.
[4] *Ibid.* 1869.
[5] *Ibid.* 1875.
[6] *Transactions of the Medical Society*, vol. xxvi.
[7] *Practitioner*, August 1906.

PAPER NO. XX

SOME FURTHER INVESTIGATIONS AND OBSERVATIONS UPON THE PATHOLOGY OF RHEUMATIC FEVER

(Reprinted from the *Lancet*, June 4, 1910)

Further criticisms of our previous communications are dealt with in the first part of this paper, and answered so far as lay in our power by counter-statements and further investigations. Indirect support of the earlier papers was now forthcoming in the researches of Aschoff, Tawara, and Carey Coombs upon the myocardium in rheumatism. Reference to our second paper in this book will show that these authors had elaborated the cardinal facts recorded there, and in so doing had corroborated the accuracy of the observations. Through the kindness of Dr. Lauriston Shaw and Dr. A. F. Hertz we were able to investigate a case of rheumatic hyperpyrexia, and the result of this research is given.

A further step in the study of the tonsils suggested by Mr. George Waugh is described, and the production of chronic forms of arthritis by means of the diplococcus recorded.

It is now close upon ten years since we published in the *Lancet*[1] the first evidence that we had at our disposal upon the pathology of acute rheumatism, and while bringing forward some additional points we would shortly review the position as it seems to us to stand to-day.

In our first paper we attempted to show the relation of our own investigations to those of others, and with this we need not deal again here; in our later papers we also referred to the researches of other workers upon this subject, notably Dr. E. W. Ainley Walker,[2] Dr. W. Vernon Shaw,[3] and Professor J. M. Beattie.[4] Much interesting criticism has been directed against the two main conclusions we have so often stated, and which we venture to repeat here: first, that a diplococcus, streptococcus, or micrococcus is a cause and most probably

the only exciting cause of acute rheumatism ; secondly, that acute rheumatism may be a cause of simple and malignant endocarditis. We will at once clear the ground by adding that we are as convinced now as we were before that both these conclusions hold good. Some of the criticisms that have been put forward have been already answered, and in this paper we shall attempt to deal further with one of the most recent of them.

It has been suggested that we have been describing an agonal or terminal infection, but we have brought forward conclusive evidence to show that some of the patients from whom the micrococcus was isolated lived for many weeks afterwards, and that others were alive and at work some years later. This criticism may then be dismissed once and for all. Again, it has been suggested that the micrococcus may be present in complicated rheumatism as an epiphenomenon, as a cause, that is, of the complications. Having produced experimentally the important lesions of the disease,[5] we naturally ask in return what is to constitute acute rheumatism.when deprived of arthritis, carditis, nodules, choreiform movements, and pleurisy ? We hold that there is, as in tuberculosis, only a predisposition left in the sense that there is some vulnerability of the tissues to this infection, and that there is no mysterious disease " rheumatism," which is always associated with secondary infections. The idea that rheumatism produces arthritis, but that a secondary infection produces the endocarditis which is so often associated, may now be looked upon as contrary to all accurate knowledge. Another difficulty has been raised that this micrococcus is not constantly present and that we have even ourselves not always succeeded in isolating it. This is naturally a troublesome question to answer, and it has been added, that when, on the one hand, some observers are repeatedly finding this micrococcus, and others of equal reputation are always failing, the success of those who obtain positive results is somewhat suspicious.

If, then, we fail to find the infective agent we must be convicted out of our own mouths, and if we find it we are suspects because others do not succeed.

With regard to this micro-organism, all our own investigations go to prove that it is very constant. We have not demonstrated it in every case of acute rheumatism, but that is no

proof that it may not be present, and, on the other hand, we have succeeded so repeatedly that we believe that we are in the position to say that if in any case one had unlimited scope and time for investigations the results would be quite constant. It is abundantly clear that we must choose the cases with care, and with a knowledge of pathological processes, selecting those in which the disease is active. It is a hopeless undertaking to investigate a case of chronic rheumatic heart disease which has been *in extremis* from secondary cardiac failure of mechanical origin, the result of the scars of former disease. Again, from one's knowledge of rheumatism, it is hardly likely that 10 cubic centimetres of blood taken at random from the general circulation is going to yield a positive result in a mild rheumatic arthritis.

The particular points that we wish to lay stress on now with reference to the isolation of this micrococcus are that we have upon several occasions demonstrated it in fatal rheumatism when it has been simultaneously found by others in the same case; secondly, that we have worked with it when isolated not by ourselves but by others; and lastly, that we have isolated it from pericardial fluids obtained from fatal pericarditis by others who have forwarded to us the fluids in sealed tubes. These tubes we have incubated without opening, and as was the case in the first result we ever reported, the diplococcus was found in these fluids after incubation—that is, growing in the natural medium.

Example No. 1. A girl, aged 7 years, was admitted to University College Hospital on March 25, 1906, with a three weeks' history of acute malaise, vomiting, and multiple arthritis. Chorea and severe pericarditis developed with endocarditis, and death occurred after barely four weeks' illness. There had been a previous attack of rheumatic fever at five years of age. The post-mortem investigation showed pericarditis of the usual rheumatic type.

Dr. F. H. Thiele, clinical pathologist to University College Hospital, obtained a pure growth of a diplococcus from the heart's blood. Dr. T. Lewis demonstrated a diplococcus in the pericardial fluid. We also found it in the exudation, and in the laboratory it conformed to the characters of the diplococcus rheumaticus, and on experiment produced multiple arthritis and pericarditis of the usual type.

Example No. 2. In June 1908, Dr. J. Graham Forbes, bacteriologist to the Hospital for Sick Children, Great Ormond Street, isolated a diplo-streptococcus during life from the blood of a child in the hospital suffering from carditis, chorea, and nodules. This diplo-streptococcus had the usual appearances and growth on culture. Dr. Forbes kindly sent us a sub-culture and with it we repeated an experiment we have under-taken before—the subcutaneous inoculation of a large dose of the culture. No suppuration resulted and in a short time all signs of an inflammatory reaction had disappeared as in our previous experience.

It is interesting that the subcultures from this case growing on unsuitable media showed a transition of the diplococcus into bacillary forms. Those who have followed the researches upon Achalme's bacillus will remember that in the last few years it had been observed this bacillus may assume a diplococcal form.

Example No. 3. Dr. A. Salisbury Macnalty, resident medical officer at the Brompton Hospital for Diseases of the Chest, in April 1909 kindly sent us a culture of a diplococcus which he had isolated post-mortem from a case of rheumatic pericarditis. This micro-organism showed the usual characters of the diplococcus rheumaticus and produced a transitory arthritis of the right knee-joint on intravenous inoculation into a rabbit.

Example No. 4. In August 1909, through the kindness of Dr. Lauriston Shaw and Dr. A. F. Hertz from Guy's Hospital, pericardial and cerebro-spinal fluid were taken from a case of fatal rheumatic hyperpyrexia and were forwarded to us in sterilised sealed tubes ; the results are fully detailed later in this paper.

We believe that these examples will dispose of any suspicion that our success in isolation of the diplococcus is dependent upon some mysterious chance, and we need only recall the work of Ainley Walker, Vernon Shaw, and Beattie in this country to make it clear that the diplococcus is an entity.

With regard to the specificity of this micro-organism we would again repeat that in our experience no other can be found in the rheumatic lesions in man which will produce similar lesions in animals. Undoubtedly various micrococci may, for example, produce experimental endocarditis, as they may also produce endocarditis in man, but various

micrococci are not found in human rheumatic endocarditis which will reproduce the disease. Again, various infections may cause experimental pericarditis, but only one in our experience can produce rheumatic pericarditis in man and also experimental pericarditis. We hold, too, that Triboulet, Wassermann, Walker, Vernon Shaw, Beattie, and ourselves have shown that the general characteristics of this streptococcus are as well differentiated as those of other members of this group. It would, nevertheless, be wrong to ignore the recent investigations by Rosenthal and others in France upon Achalme's bacillus, or to hide the fact that they claim that they have proved its causal relation to the disease. We can only repeat that we have failed to demonstrate this bacillus, and would add that even the French observers lay stress upon its pleomorphism and its occurrence in *diplococcic form.* Thus Rosenthal [6] mentions the reception of a diplococcus from Belgium which had been isolated from the blood of a case of active rheumatism. This, when transferred to his anaerobic media, developed into the bacillus of Achalme, but in aerobic culture it retained its diplococcal form. Rosenthal and others each year that passes are apparently striving to prove that this diplococcus is the bacillus of Achame growing in unsuitable media. We, on the other hand, maintain that the diplococcus grows naturally in aerobic media, but may, as we stated eight years ago, when growing in unsuitable media, assume bacillary forms. Whether these bacillary forms are Achalme's bacillus we cannot say.

In this country we believe the tendency has been to mystify the main question—the ætiology of rheumatism—by introducing a classification of the streptococci by certain sugar ferment tests in the laboratory. Apparently, as an outcome of this, we have to be satisfied with the description of a streptococcus salivarius or fæcalis. That a streptococcus in the saliva or fæces should give certain tests in the laboratory is not likely to be of any practical moment unless some peculiar streptococci develop *de novo* in these situations. Seeing that the nature of this group of micro-organisms is much altered by the media in which they grow, such a classification is in our present state of knowledge most perplexing. Instance, for example, the diplococcus of rheumatism: it undoubtedly locates itself in the tonsils, but are not these washed by the

saliva, and is not the saliva swallowed into the stomach and passed into the intestines with the food? Which is of the greater importance—that a diplococcus can be isolated from a rheumatic angina and reproduce rheumatic lesions, or that a diplococcus isolated from the saliva and fæces can give some apparently specific sugar tests in a laboratory? Lastly, what alterations in character and virulence might not the diplococcus undergo when, dislodged from the tonsils by the saliva, it lingers in a new environment such as the fæces?

Is it not an outcome of the confusion which arises from such a classification that in a valuable paper on infective endocarditis we read as follows: "It would obviously be fallacious to conclude that any micro-organism isolated from the blood of a patient with fever, endocarditis, and chorea had any necessary connection with the cause of rheumatic fever"? Seeing that a streptococcus isolated from acute rheumatic lesions, and let us add also from the blood in acute rheumatism, can produce endocarditis, fever, and choreiform movements, as more than one skilled bacteriologist has shown, it is difficult to see how the conclusion that this streptococcus has some necessary connection with rheumatic fever can obviously be fallacious. It may be a wrong conclusion but it seems a reasonable one.

Indirect Support from Recent Investigations

We would next point out that in the last ten years the trend of scientific investigation and clinical observation has strengthened our position in spite of the fact that some of these observations have been made by those who have not had the causation of rheumatism in view, and others have been made by those who have not accepted our explanation and yet have been of assistance in bringing us support by their independent observations.

To take the first type of evidence, we would allude to a paper written by one of us in 1898 and read at the Royal Medical and Chirurgical Society (Paper No. 2).[7] In this contribution it was demonstrated that in rheumatic carditis scattered foci of inflammatory change were to be found in the connective-tissue framework of the heart springing from the region of the small blood-vessels. It was further shown that in these regions gross changes might be found in the neighbouring

muscular fibres. This distribution, it was pointed out, strongly favoured the view that they were a result of some bacterial infection. Later, when we identified the infection, we produced and showed at the Pathological Society of London experimental carditis of the same order.[8] These observations have been expanded, notably by Aschoff and Tawara [9] and Carey-Coombs,[10] who have maintained that they are specific lesions, and their importance has been insisted upon from an entirely different standpoint to ours. We emphasised their importance as a factor in the heart failure of rheumatic morbus cordis. Others, led by Dr. James Mackenzie, have dwelt upon their importance in connection with cardiac arrhythmias and the primitive cardiac muscle. If we recall that Keith, in one of his latest papers which he read upon the anatomical side of this question before the Medical Society of London in 1909, stated his conviction that cardiac nerve and cardiac muscle come into such close relation that they may fairly be said to merge in the primitive muscular fibre of the cardiac tube, it becomes at once apparent that these focal lesions of rheumatic carditis must have an important bearing upon this aspect of cardiac disease.

Since Aschoff published his observations they have attracted considerable attention in this country not because of their bearing upon the ætiology of rheumatism, but because they are concerned with the ever fascinating problem of the heart-beat.

Next we will take the second type of evidence supplied by others who are opposed to our explanations, but who in spite of this have given us indirect support.

To us there are few more curious points in the history of cardiac pathology than the attitude held by many toward rheumatic endocarditis. They admit it is infective; the evidence, indeed, in its favour is overwhelming, but they hesitate to admit that this endocarditis may become malignant. When, however, we analyse the meaning of this malignancy as applied to endocarditis, we find it expresses an inability on the part of the damaged tissues to overcome the local infection. There may be partial, and exceptionally even complete, success, but the rule is failure. This malignancy is, then, no new mysterious change in the tissues, and as its antecedent we find the most frequent is previous rheumatic endocarditis.

Now come the curious conclusions we are asked to accept :

firstly, that an infection in the endocardium of rheumatic origin is always simple—that is, is always capable of healing ; and, secondly, that malignant endocarditis after rheumatism is always caused by a secondary infection of valves scarred by previous disease.

The first conclusion is strange, because infections of the rheumatic type are not likely to be always "simple" ; they clearly vary in virulence as do all other infections of the same group. The second conclusion that bacteria prefer scarred valves is, in our opinion, a false one. There is no evidence that bacteria prefer scar tissue ; in fact, all evidence is against it. If the so-called scarred valves of rheumatism are examined it will be found that the vegetations are not really scar tissue, but are masses of unhealthy necrotic material which the scar formation has not invaded. We hold that in this necrotic tissue the rheumatic infection that caused the original endocarditis often lurks quiescent but not destroyed. The formation of scar tissue makes it difficult for leucocytosis to deal with bacteria in these isolated necrotic patches, which, bordering as they do on the general circulation, are as much a source of danger as a necrotic gland close to the circulation is in tuberculosis.

The recent vegetations of rheumatism are, in our opinion, often much more chronic than is generally believed, and those who investigate them from this point of view will find in them areas of necrotic tissue shut off by scar tissue—that is, they will find imperfect healing. We believe that in cases of malignant endocarditis of rheumatic origin the disease has been slightly active long before symptoms call attention to the serious nature of the disease. This link in the chain of evidence is difficult to get, but doubtless it will be obtained by clinicians who keep a constant watch on their patients who leave hospital with rheumatic heart disease. When in these cases the malignant type arises it is not necessarily because some added infection has attacked scar or sclerotic tissue, but because some agency lowering the general health has aroused the lurking micrococci of a previous infection which are lying in the necrotic areas bordering on the general blood stream.

In our original paper [11] we could not hazard how many cases of malignant endocarditis were rheumatic, but we thought future experience would show that a very considerable

percentage would prove to be of this type. We are thus interested to find a writer discovering that the type of streptococcus most often found in infective endocarditis is not the highly pathogenic streptococcus of suppurative processes, but what he terms "one or other of three types of streptococci that are more closely allied to the 'saprophytic' streptococci of the alimentary canal." In an analysis of 100 cases of infective endocarditis we also note that he finds a streptococcus was present in 62. We hold that all complete evidence goes to show that the streptococcus which causes acute rheumatism is a cause also of malignant endocarditis, and that the further evidence in this condition of the frequent occurrence of "streptococci," which for want of a better description from others we may call peculiar, is an additional support to this view.

We would add that since our first contribution to this question we have seen further cases in adults and children which confirm our original examples and entirely support the view that rheumatism may be a cause of malignant endocarditis.

Acute Rheumatism and Rheumatic Fever Faulty Terms

The next point we would emphasise is the retarding influence that the terms acute rheumatism and rheumatic fever exert upon the study of rheumatism. If we compare any one other great infection to rheumatism in its clinical course it would be tuberculosis. This is but a repetition of a former statement, but we allude to it now because it is so thoroughly supported by a recent paper by Dr. R. Miller [12] upon chorea. In this paper the writer dwells upon the fact that the choreiform movements are but the developed disease, and that there may be warnings weeks before these appear. The late Dr. W. B. Cheadle, Sir Thomas Barlow, and Sir Dyce Duckworth have called attention to the same point. This premonitory stage is not peculiar to chorea, for heart disease and arthritis show the same features. Many cases in childhood which develop obvious rheumatism may suffer for some weeks from fever, anæmia, and debility before anyone can foresee the exact meaning of these symptoms, a point which, we may add, Dr. G. H. M. Dunlop has also insisted upon. How can we, in face of these facts, keep the terms acute rheumatism and rheumatic fever as indicative of anything but phases of rheumatism? We have

no doubt that a good deal of the mystery of unexplained heart disease, and in particular mitral stenosis, is the result of this imperfect naming of the disease. It is essential that some more general term such as rheumatism, which implies neither acuteness nor chronicity, should be used.

Rheumatic Hyperpyrexia

Hyperpyrexia is an event in rheumatism which all would point to as one which should throw light on the pathology of the disease. Through the kindness of Dr. Lauriston Shaw and Dr. A. F. Hertz we have had assistance from Guy's Hospital upon this question. Until this recent opportunity we had only one case for investigation, and that not a classical example. It was fully published by us in the *Lancet* in 1905 (Paper No. 18) [13] and was peculiar in that there was severe cerebro-spinal meningitis. In the exudation there were great numbers of strepto-diplococci, and we satisfied ourselves that it was a rheumatic case. There is no necessity to recount the details of that investigation here. Our second from Guy's was of the classical type, the patient, an adult, dying with a temperature of 107° F., and the post-mortem examination showing active rheumatism but no meningitis. The following details give the salient features of this investigation.

The following tubes, among others, were received from Guy's Hospital on August 13th, 1909: (1) the turbid pericardial fluid in a sterilised pipette; (2) the blood; and (3) portions of the cerebral cortex. The two latter were placed in bouillon. The pericardial fluid was incubated overnight without addition of any medium.

The following results were obtained. A pure growth of strepto-diplococci was present in the incubated pericardial fluid. The *cerebral cortex* gave a growth of diplococci with a few colonies of staphylococcus aureus. The *blood* gave a growth of diplococci and bacillus coli. A film of the cerebro-spinal fluid showed a few diplococci. A film of the pericardial fluid showed the diplococci in streptococcal chains and in considerable number.

On August 15 two intravenous inoculations were made into rabbits. No. 1 received 30 drops of the pericardial fluid. No. 2 received 20 drops of the bouillon culture from the cerebral cortex which contained some colonies of staphylo-

coccus aureus with the diplococcus. The second rabbit died in 24 hours from acute pericarditis; and the pericardial fluid from this, incubated overnight, showed a pure growth of strepto-diplococci. The other organs showed no obvious change. They were not soft and there were no hæmorrhages. The first rabbit lived a week and during that time it rapidly wasted and developed pyrexia, endocarditis, and arthritis of the right knee-joint. The post-mortem examination showed early endocarditis of the tricuspid valve, a fibrino-plastic exudation in the right knee-joint, and an infarct in the right kidney. Cultures from the right knee-joint gave a pure culture of strepto-diplococci.

A third rabbit was inoculated intravenously with 10 minims of the incubated pericardial fluid from rabbit No. 1. Three days later there was arthritis of both shoulder-joints with wasting and general illness, but during the next week there was gradual recovery from the arthritis. This animal died from acute intussesception 12 days after the injection, and the post-mortem examination showed no cardiac lesion and a healing arthritis.

A fourth rabbit was inoculated on August 25 with a culture from the cerebro-spinal fluid. On the 28th the right knee became swollen and tender and the animal began to waste. No cardiac lesion was detected.

Examination of fragments of the aortic and mitral valves, portions of the motor cortex and pia mater of the patient showed that the valvular lesions were of old standing and that the brain and pia mater examined only showed a few diplococci.

The result of this investigation may be thus summarised : From a case of rheumatic fever with carditis, arthritis, and hyperpyrexia a strepto-diplococcus was obtained in pure culture direct from the pericardial fluid incubated overnight. This strepto-diplococcus produced, on intravenous inoculation into rabbits, non-suppurative multiple arthritis, pericarditis, endocarditis, and infarction, and the micro-organism was again isolated from the lesions in pure culture. The same micro-organism was present in the cerebro-spinal fluid, motor cortex, and blood of the patient.

It would be a mistake to infer too much from a single case, but we believe this investigation supports the general opinion

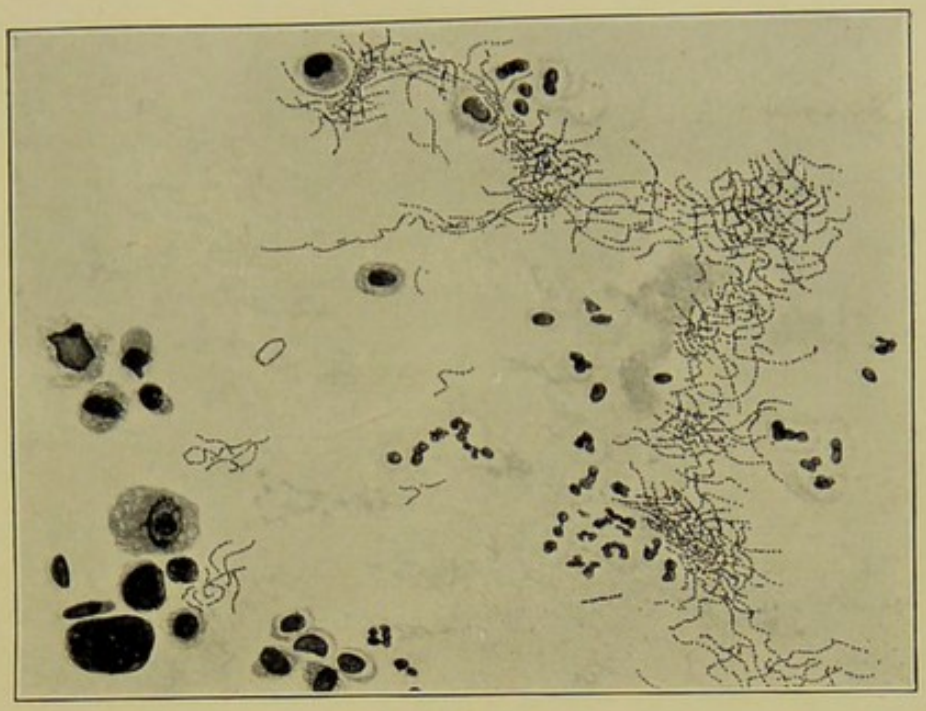


FIG. 84

Incubated human pericardial fluid (× 600) from a case of rheumatic pericarditis and fatal hyperpyrexia. The diplococcus growing in streptococcal chains

FIG. 85

Incubated pericardial fluid of a rabbit dead from pericarditis resulting from intravenous inoculation with the diplococcus isolated from the case of rheumatic hyperpyrexia. (× 1000.)

among physicians that rheumatic hyperpyrexia is a peculiar toxæmic process rather than an intense bacterial invasion, for although the micrococci were both isolated and demonstrated, they were not present in the tissues or blood in any extraordinary numbers.

Investigations upon the Tonsils in the Rheumatic

Two other lines of investigation have occupied our attention in the last five years : the first is another step in the study of the tonsils suggested to us by Mr. George Waugh ; the second is an experimental study of arthritis, with a view to ascertaining whether more than one form of arthritis may result from intravenous inoculation of the same micro-organism. The object of this second investigation is to widen the field of study of rheumatoid affections, reversing, as it were, the usual method of inquiry. The clinician seeks among this heterogeneous group to find some one clear path. We have started along one clear path (the study of the diplococcus) and endeavoured to find our way some little distance into this heterogeneous group.

Taking first the tonsils in rheumatic fever we need only mention the great frequency of tonsillitis in this disease, and the demonstration by Dr. William Hill [14] some twenty years ago of deep-seated foci of disease in enlarged tonsils removed from the rheumatic. In 1900 we showed that a micrococcus found in rheumatic lesions could be isolated from acute rheumatic angina, and be demonstrated in the tonsils, and further would produce similar lesions. In the next year Fritz Meyer published an extensive paper upon the same subject, and we have returned to the question again to work out Mr. Waugh's suggestion. Mr. Waugh advocates enucleation of the large unhealthy tonsils that are so often present in rheumatic children, and in some carefully chosen cases has done this for us between the rheumatic attacks. These tonsils were seared on removal, cultures were taken from their depths, and the histological appearances of them investigated. One example will suffice to show the kind of case investigated, six of which have been examined up to the present date.

The patient, a male aged 10 years and 5 months, came to the Hospital for Sick Children, Great Ormond Street, in February 1908, suffering from slight chorea and rheumatic pains. In 1906 he had an attack of rheumatic fever, since

which he had never quite recovered his usual health, and had always had shortness of breath on exertion. The heart was obviously affected. There was considerable mitral regurgitation, with hypertrophy and dilatation. In addition he had two very large tonsils and was subject to sore-throats. The cervical glands showed a moderate enlargement. In April, when quite recovered from his active rheumatism, Mr. Waugh enucleated both tonsils. Immediately after removal the surface was seared, and cultures were taken from the centre of one gland. Histological examination by section and films of the other tonsil showed the presence of streptococci in the deep part of the gland. The culture gave an almost pure growth of strepto-diplococci, from which it was easy to isolate this organism in pure culture. Five minims of this culture injected intravenously into a rabbit produced no result. Two cubic centimetres produced arthritis and fatal aortic endocarditis. One cubic centimetre in another experiment produced arthritis of the left knee, which slowly recovered. Subsequently smaller doses produced arthritis of the right knee-joint and fatal endocarditis.

We have here but a repetition of the results obtained in our original case in 1899, and independently confirmed by Fritz Meyer[15] in 1901. The particular point of interest lies in the fact that here we are dealing with tonsils in the rheumatic when they are not in the stage of acute inflammation, during an attack of acute rheumatism, but in the latent period after previous attacks of the disease.

There can be very little doubt, we believe, that these large unhealthy tonsils are a constant menace to the rheumatic, and that these investigations originated by Mr. George Waugh show decisively that there abound in the depths of these disordered tissues strepto-diplococci which will produce with much constancy in appropriate dosage endocarditis, pericarditis, and arthritis on intravenous injection into rabbits. We believe they may well explain some rheumatic relapses. The relation of acute rheumatism and tonsillitis to the diplococcal infection is now so well defined by clinical observation, histological investigation, and experimental research that it constitutes one of the most satisfactory advances in the study of the disease. We have only to contrast the explanation it gives us with the older nervous and lactic acid theories to

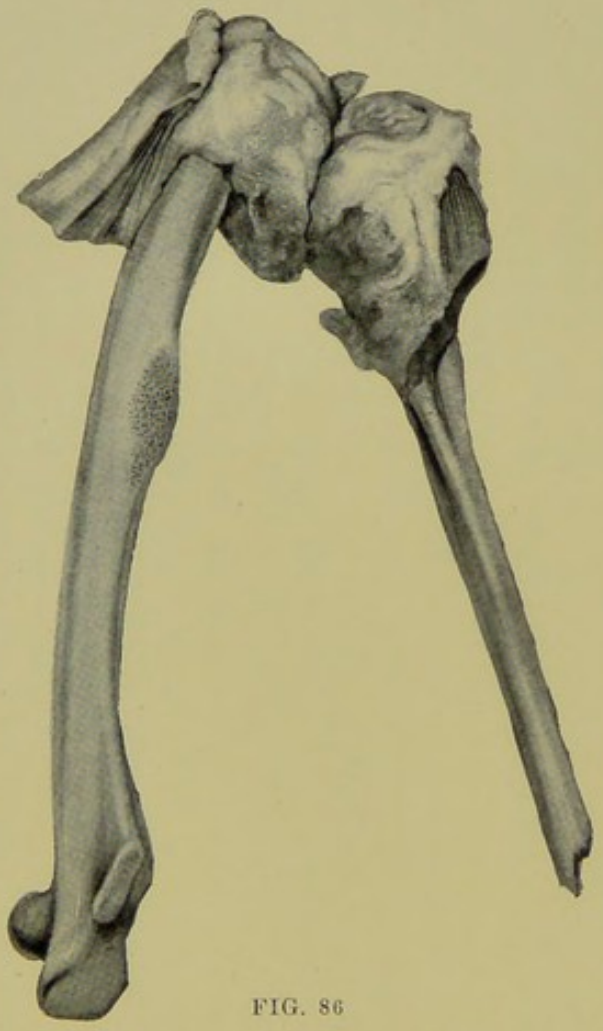


FIG. 86

The knee-joint, femur and part of the tibia of a rabbit that was killed after suffering from chronic arthritis for eighteen months. The knee-joint showed extensive non-suppurative osteo-arthritis. A point of particular interest illustrated by this figure is the presence of a periosteal nodule of considerable size at the junction of the upper two-thirds with the lower one-third of the shaft of the femur. There was a similar node on the middle of the shaft of the other femur. The result of intravenous inoculation with the diplococcus.
(From the museum of University College Hospital.)

FIG. 87

A photograph showing the radius and ulna from two rabbits. Those on the right side of the figure are normal. The ulna on the left side shows extensive osteo-arthritic change the result of chronic arthritis from intravenous inoculation with the *Diplococcus rheumaticus*. The lesion was non-suppurative.

realise this advance, which is one, not only of scientific interest, but also of practical importance. We have not investigated other pathways of infection, but great attention has been directed to the importance of unhealthy condition of the teeth. It would be wrong to deny, too, the possibility of infection from the alimentary canal, but we do not think that at present the wide acceptance of auto-infection from the intestines in arthritic diseases has as yet been completely justified by the evidence that has been forthcoming, however probable it may seem on clinical grounds.

When the position of the tonsils is borne in mind it may seem a startling assertion to make that strepto-diplococci may be obtained in pure culture from the depths of the diseased glands, yet it is true, and has happened not only in our experience but in one case was quite independently ascertained by Dr. Graham Forbes, who had examined a culture from the same case.

We are not pretending that a pure culture is a constant result, but we have invariably found that the strepto-diplococci predominated. Again, we do not deny that the same results, both cultural and experimental, might obtain if diseased tonsils from the non-rheumatic were treated in the same way. We have not worked at this point. Should similar results obtain it would not negative the interest of the facts before us, for it is quite evident from our clinical knowledge that there must be a tendency to develop rheumatism, and we have never believed that the exciting cause was not present in the normal throat. As with tuberculosis and pneumococcic infections, so with rheumatism, there are many factors to be considered in addition to the presence of a bacterium.

Investigations upon Arthritis

When the diplococcus of rheumatism is injected intravenously it produces arthritis with great frequency; and further we have convinced ourselves that it may produce it in various forms. In 1902 [16] we published with drawings in the *Transactions of the Pathological Society* a short paper upon the production of an osteo-arthritis—non-suppurative in character—by the intravenous inoculation of a micrococcus isolated from a case of human osteo-arthritis in which death had occurred from misadventure. We believe this to have been the first

recorded example of experimental osteo-arthritis by intravenous inoculation. Since that date we have produced osteo-arthritis and peri-articular arthritis with the diplococcus rheumaticus, and at the present time we have a very striking specimen of an arthritis resulting from this infection. This occurred in a rabbit which had developed inflammation first of one knee-joint and then of the other, from which it gradually recovered, but eighteen months later, though in good health, it limped to some extent upon the hind limbs. This specimen showed that there was a clear fluid in both articulations, but the right patella was dislocated and had formed for itself a new facet on the inner side of the internal femoral condyle and the original facet had lost much of its cartilage, and the bones had been eroded. The left joint showed erosion of cartilage. This specimen is in the museum of the Royal College of Surgeons. The occurrence of dislocations of joint surfaces in human "rheumatoid arthritis" is well recognised, and the production of such a deformity is strictly analogous to the condition in the specimen just described, in that there are in both a stretching and damaging of the capsules of the articulations by a non-suppurative process, a damage to the articulating surfaces themselves, and a faulty pull of tendons connected with the joints. At the British Medical Association meeting at Manchester we also demonstrated convincing examples of the "guttering" of osteo-arthritis, and published illustrations of these changes in a paper in the *Medical Press and Circular*.[17] In this paper we also showed that perivascular fibrosis occurred in the capsules of articulations, the subject of experimental and pathological chronic arthritis, explaining thereby the "withering" of joints in rheumatoid affections. We have also produced that rarefying osteitis of bone ends in the neighbourhood of joints affected by chronic disease which is well recognised in "rheumatoid arthritis."

In conclusion, we would repeat that no explanation of acute rheumatism can, we believe, compare with that which attributes it to an infection with a diplococcus of the streptococcal group; and that although during the last ten years this view has gained but little headway in this country the Chelsea Clinical Society in 1900 marked a forward step in London when they opened a discussion on "Acute Infective Rheumatism."

REFERENCES

[1] *Lancet*, September 22 and 29, 1900.

[2] Ainley Walker, *Practitioner*, 1903.

[3] Vernon Shaw, *Journal of Pathology and Bacteriology*, 1903.

[4] Beattie, *Brit. Med. Jour.*, December 1904 ; *Journal of Experimental Medicine*, vol. ix, No. 2, 1907.

[5] *Transactions of the Pathological Society of London*, 1901. *Lancet*, May 4, 1901.

[6] *La Tribune Médicale*, February 26, 1910, p. 134.

[7] Poynton, *Transactions of the Royal Medical and Chirurgical Society*, vol. lxxxii, 1899.

[8] *Transactions of the Pathological Society of London*, 1901 ; *International Clinics*, vol. iii, Series 13.

[9] *Brit. Med. Jour.*, 1906, vol. ii, p. 1103.

[10] *Quarterly Journal of Medicine*, vol. ii, No. 5.

[11] *Transactions of the Royal Medical and Chirurgical Society*, vol. lxxxv, 1903.

[12] *Lancet*, December 18, 1909, p. 1808.

[13] *Lancet*, December 16, 1905, p. 1761.

[14] "Tonsillitis in Rheumatic States," 1889.

[15] A paper read before the Congress of Internal Medicin, Berlin, 1901.

[16] *Transactions of the Pathological Society of London*, 1902.

[17] *Medical Press and Circular*, April 5, 1907.

PART II

SUB-GROUP E

THE THREE PAPERS IN THIS SUB-GROUP ARE IN THE MAIN CLINICAL IN CHARACTER, THE FIRST TWO DEALING RESPECTIVELY WITH RHEUMATISM IN VERY EARLY LIFE AND WITH THE ASSOCIATION OF SCARLET FEVER AND RHEUMATISM. THE THIRD PAPER TREATS IN PARTICULAR OF RHEUMATIC HEART DISEASE AS AN EVENT IN THE HISTORY OF AN INFECTIVE PROCESS RATHER THAN AS A PARTICULAR FORM OF CARDIAC AFFECTION

PAPER NO. XXI

A CONTRIBUTION TO THE SUBJECT OF RHEUMATISM BASED UPON A STUDY OF FIFTY-TWO CASES IN CHILDREN UNDER FIVE YEARS OF AGE, AND AN ANALYSIS OF ONE HUNDRED CASES OF FATAL SUPPURATIVE PERICARDITIS IN CHILDHOOD

(Reprinted from the *Quarterly Journal of Medicine*, April 1908)

This short clinical paper demonstrates that acute rheumatism is not infrequent at five years and even under that age. The suggestion that there is any peculiarity in the age incidence of this disease which militates against the theory of its infective origin is thus disposed of, and its identity at this age with the condition in later life established. Finally, a study of pneumococcic pericarditis gives a striking proof of the great differences in the effects of the pneumococcic and rheumatic infections upon the heart, and shows that, though the diplococcus of rheumatism in vitro *would appear to be, in some respects, closely akin to the pneumococcus, yet in their pathogenic properties in the human tissues these micrococci are essentially different.*

THERE has been a good deal of difference of opinion expressed by writers as to the frequency of acute rheumatism in children under five years of age. Some have maintained that it is an exceedingly rare occurrence, while others have doubted this. The question is one of theoretical and practical importance, and this is the excuse for putting on record here our own experience as a contribution to the subject of acute rheumatism.

The theoretical interest lies mainly in our conception of the cause of acute rheumatism, or, as we would prefer to call it, rheumatism. If, as one is now almost compelled to admit, there is an infective agent, or, in the opinion of many, more than one, which determines the active disease, it is difficult to

understand why, during the first five years of life, the occurrence of the infection should be very unusual. It may be reasonably admitted that prior to school life there is less exposure to the infection, but even then, one can hardly help believing that a sufficient number of cases must be met with to enable us to recognise that rheumatism does not make a mysterious appearance at any particular age, but is throughout life a menace to some constitutions. If this should prove to be the case, it will help us to bring the rheumatic infection into line with such other great infections as the pneumococcic and tubercular.

In a symposium upon rheumatic fever in childhood, the result of a recent Congress in America, we find one writer has the hardihood to suggest that in England a disease in children has been manufactured which we call rheumatism, by fitting together all manner of divers symptoms. This procedure, according to him, has been adopted to account for the disease up to the age of twelve years ! No one in this country has any qualms as to the reality of the disease from five to twelve years, and this unguarded writing can only be a warning to those who live in a different country and attempt to criticise the clinical acumen of physicians who have special advantages in any particular line of investigation.

In rheumatism at this early age there are several points of practical interest. The question of diagnosis is one, for under five years of age such widely different disorders as scurvy, anterior poliomyelitis, spinal caries, congenital syphilis, gonococcic and meningococcic arthritis, congenital heart disease, influenzal and pneumococcic septicaemia come into the field of discussion. This particular aspect of the question we shall not consider here, for it is dealt with in many books.

Another point is the clinical character of the disease at this early age. Shall we find this unusual, or closely resembling the character in later childhood and adolescence ? The death rate, the percentage of cardiac affections, and the liability to relapse, are other details of importance.

Lastly, shall we be led from a study of such cases to the view that rheumatism is not an entity, because we find that at this age its differentiation from other infections becomes so difficult as to degenerate into a mere academic splitting of hairs ? Upon this point we have been at some pains to collect

for comparison 100 fatal cases of suppurative pericarditis under twelve years, mostly the result of pneumococcic infection. Our object has been to study side by side with rheumatism, which we regard as an entity, an infection which approaches it bacteriologically and clinically.

There are 52 cases of rheumatism in children under five recorded in this paper. Many of the notes are fragmentary. They have, however, this value, that they are all personal observations, not one is taken from hearsay evidence, and as such they assist in establishing the main thesis of the paper, that the frequency of rheumatism in children under five is sufficient to make one believe that it obeys the laws of other great infections.

To these 52 cases are appended 17 others. These are older children, who have come with rheumatism, and whose parents have given a history of an earlier attack before the age of five. In the case of chorea, the evidence when repeated in several instances is very suggestive of truth, for chorea makes a deep impression upon the minds of parents. The 52 cases, and 17 presumptive ones, are placed in appendices at the end of the paper, and, in order to avoid wearisome reiteration, the chief points that they illustrate are considered in the short summaries that follow. There can be, we think, no doubt that the fact that we have been able to collect, in a desultory fashion, 52 examples of rheumatism under five years, all of which have been under personal supervision, settles the question that rheumatism resembles other great infections in having no mysterious age limit.

It is equally clear that the disease before the age of five years resembles very closely the condition from five years to adolescence, for if we take these 52 cases and choose those manifestations of acute rheumatism that are generally accepted as cardinal, such for example as heart disease, arthritis, chorea, sore throat, and nodules, we find the following figures :

Definite heart disease . . .	in 43 cases
Arthritis or arthritic pains . .	in 35 ,,
Chorea	in 18 ,,
Sore throat	in 10 ,,
Nodules	in 8 ,,

The mortality is high at this early age. Eight died, and

five more were in a hopeless condition. Twenty-two made partial recoveries with permanently damaged hearts, and among these it is more than probable that some succumbed later to further attacks.

A terminal pericarditis was present in seven out of the eight fatal instances, and there were in these cases many other manifestations of rheumatism, the disease generalising as it does in other infections in childhood. Yet, in spite of the systemic involvement and terminal pericarditis, it was impossible to mistake the condition for any other than rheumatism. In support of this we submit the analysis of 100 cases of suppurative pericarditis in childhood, the great majority of which were pneumococcic in origin. In 15 of these the bacteriological nature of the condition was accurately ascertained as pneumococcic. Eight were probably not of this nature, being associated with acute osteo-myelitis, otitis media, and suppurating wounds, and in these there were multiple pyæmic abscesses.

One example of a characteristic case will throw into relief the differences in the clinical course of a rheumatic and pneumococcic pericarditis. A. C., a female aged $2_{1}^{3}_{2}$ years, had suffered for several weeks from whooping cough, followed by pneumonia. When she came under observation she was very cyanosed and dyspnœc. Respiration was panting, and there was irregular fever. Both sides of the chest showed signs of effusion, and later in the illness the cardiac dullness was found increased; and the sounds were noted to be faint. Double empyema was diagnosed and suppurative pericarditis suspected. Death occurred rapidly, and $1\frac{1}{2}$ ounces of pus were found in the pericardium, together with pus in both pleuræ. The pneumococcus was isolated from the effusion. Thus, in this case, associated with this form of pericarditis, there were purulent pleural effusions, but there was no arthritis, and, still more striking, there was no endocarditis.

Rheumatic pericarditis is, on the whole, easy of diagnosis, but few conditions are more difficult to detect than suppurative pericarditis. In only six of the 100 cases was it detected with certainty, and two of these showed the rare symptom in suppurative pericarditis of pericardial friction.

The reasons for the difficulty in diagnosis help us to emphasise the distinctions between rheumatic and pneumococcic

pericarditis. Thus the occurrence of friction in two per cent. of the latter series is a very different experience to its frequency in the rheumatic form.

The absence of endocarditis is even more remarkable, only one per cent. of the pneumococcic showed any valvular lesion. Again, in only one of these cases was pericarditis the outstanding lesion. Three others showed evidence of old pulmonary disease. Fifty-four were associated with an empyema on one or both sides, and 31 with acute pleurisy or pneumonia. Two were complicated by acute pulmonary tuberculosis, and eight with septic broncho-pneumonia.

Pleurisy and broncho-pneumonia are met with in virulent rheumatic heart disease, but it is quite the exception and not the almost invariable rule for the pulmonary lesions to dominate in the clinical picture.

Couple this with the fact that in an analysis of 150 cases of fatal rheumatism under twelve years, 149 showed a valvular lesion, and we doubt whether two more striking proofs of the specific differences in these infections could be possible.

Nevertheless, if we turn to the age incidence, we find the most convincing additional evidence. In the pneumococcic series 84 per cent. occurred before the child reached the fourth year, and 66 per cent. between the ages of one and three years. Rheumatic pericarditis, as shown by these 52 cases, certainly occurs with some frequency under five, but this frequency rises rapidly, with the incidence of rheumatism, up to the age of ten. Pneumococcic pericarditis followed measles in 12 instances; the rheumatic is more closely associated with scarlet fever.

These fatal cases of pneumococcic pericarditis also bring out clearly that rheumatic pericarditis cannot be looked upon as a peculiar phase of those infections which produce suppuration, using that term in its everyday sense. For if we first consider rheumatic pericarditis we find an acutely virulent hæmorrhagic form, a severe form in which occurs an exudation, which we consider a rheumatic suppuration, a mild form with a clear exudation, and, lastly, a smouldering fibrino-plastic one.

If we consider the pneumococcic pericarditis we find the same variety of processes. There are the fulminating types, the severe ones with profuse suppuration, the milder ones with a more fibrinous exudation, and the undoubtedly rare but

definite cases in which there is a partial organisation of a chronic inflammatory exudation.

Although the difficulty in the diagnosis of suppurative pericarditis is almost insurmountable, and for this reason it becomes a practical impossibility to date the exact time of its onset during the course of an acute illness, nevertheless the post-mortem records show that this pericarditis may last many weeks before proving fatal, and the illnesses associated with this condition may be grouped into three classes :

1. The acute, running a course of about four weeks. This included twenty cases of the series.

2. The sub-acute, lasting from four weeks to six months. Representing 50 cases.

3. The chronic, with insidious onset, lasting from six months to one year. Representing 17 cases.

It is clear that both rheumatic and pneumococcic pericarditis show variations in virulence but it cannot be accepted that the rheumatic form is a phase of the pneumococcic.

Such clinical and pathological facts as these are far more convincing evidence of the specific nature of rheumatism than are the evidences of laboratory tests against its specificity, for they represent the behaviour of the infective agent in the media of the human tissues, which are the media with which we are concerned in human diseases. In conclusion, we would hold that rheumatism, though unusual, is by no means rare under five years, and that its study strongly supports the specific nature of the infection.

Appendix I

Fifty-two cases of Rheumatism under five years of age

Case 1. January 1899. T. W., male, aged $4\frac{11}{12}$ years. Two weeks previously he had complained of pains in the knees, followed by chorea. When first under observation there was moderate general chorea and early mitral disease. A severe attack resulted, but there was a partial recovery and the child was able to get about again. In November 1899, there was a severe relapse with fresh cardiac involvement and nodules, with wasting. This case was lost sight of, but the condition was practically a hopeless one.

Summary : Relapsing rheumatism ; arthritis ; morbus cordis ; chorea ; nodules ; outlook hopeless.

CASE 2. October 1899. E. S., female, aged 4 years. A vague history of some weeks, in which pains in the joints were complained of, and breathlessness noticed. There was a family history of rheumatism. This child had organic mitral disease. A good recovery followed. She was lost sight of.

Summary : Arthritic pains and heart disease ; good recovery.

CASE 3. November 1899. M.P., male, aged $3\frac{8}{12}$ years. This child had been living on the ground floor in a damp house, and was brought for chorea, which had been preceded by a sore throat. When first seen there were marked anæmia, chorea, and dilatation of the heart. After an illness of four months there was recovery with a mitral lesion. She was lost sight of.

Summary : Anæmia ; chorea ; morbus cordis ; sore throat ; recovery.

CASE 4. March 1900. G. M., male, aged $4\frac{3}{12}$ years. His father had suffered from rheumatic fever. There was a history of some weeks of debility, wasting, and anæmia, followed by slight chorea. When first under observation there was, in addition, dilatation of the heart. This patient made a good recovery.

Summary : Anæmia ; chorea ; cardiac dilatation ; recovery.

CASE 5. September 1900. J. M., male, aged $3\frac{4}{12}$ years. Some weeks before coming under observation this child was reported to have caught cold and developed a sore throat. There followed multiple arthritis, the ankles being first affected. When first seen there were multiple arthritis, profound anæmia, mitral and aortic disease, but no nodules. The temperature was only just above normal. Whilst under observation there was slight epistaxis, and later pleuro-pericarditis. The child died in February 1901, of heart disease. A post-mortem examination was refused.

Summary : Sore throat ; morbus cordis ; anæmia ; epistaxis ; arthritis ; death, after pleuro-pericarditis.

CASE 6. January 1901. W. G., male, aged $2\frac{1}{2}$ years. This child had already been ill for seven months. The onset had been with pains in the joints and swelling of the knees and ankles. The doctor in attendance had called it rheumatic fever. When we saw the child he was suffering from severe mitral disease, with both dilatation and hypertrophy. His brother, whom we also saw in his illness, was suffering from

unequivocal rheumatism. These patients were only brought for an opinion, and were not seen again, but the child was undoubtedly damaged for life.

Summary: Arthritis; morbus cordis; outlook bad.

CASE 7. March 1901. E. H., female, aged 4½ years. This was a very instructive example of the danger of rheumatism. Three months before, without a single definite symptom, she was noticed to be getting pale and progressively feebler. The first distinct warning was the occurrence of slight choreic twitchings. When first under observation there was striking muscular feebleness. The heart was feeble and dilated and the sounds faint. Soft pericardial friction was audible. No nodules were present. Fourteen days later thrombosis occurred in the left jugular, and the child died on March 23. The post-mortem examination showed pericarditis, multiple endocarditis, pleurisy, and broncho-pneumonia.

Summary: Anæmia; broncho-pneumonia; carditis; chorea; pleurisy; venous thrombosis; death; post-mortem examination.

CASE 8. August 1901. J. O., male, aged $4\frac{8}{12}$ years. Came under observation for arthritis. His mother had suffered from rheumatic fever. His first attack of arthritis was in January 1901, affecting the ankles and feet. This attack was followed by another in March, and a third in May. The fourth attack, in August, involved the metacarpo- and metatarso-phalangeal joints and both knees. There was irregular fever, with enlargement of the glands in the axillæ and groins. The splenic dullness was also increased. Later, more of the smaller joints were involved, and the neck and back became stiff. The heart was dilated, but there was no murmur. This case went from bad to worse, and extreme emaciation was a prominent feature. Eventually the parents took him away in disgust. A year later on inquiry, expecting to hear that the child had died, the parents informed us that after four months in bed, and treatment by cod liver oil, he improved, and was now able to go to school. Later they brought him and we found the enlarged glands were now normal, as also the splenic dullness. The cervical spine was rigid and flexed, and there was considerable periarticular thickening round the wrists. Both knee joints were enlarged and creaked on movement. More remarkable still was obvious heart disease. A loud mitral systolic murmur

was audible, and the left ventricle was hypertrophied and dilated. In 1902 there was another attack of arthritis. In March 1903, he was again brought very ill. His head was bent almost on to his chest, and his neck was swollen and stiff. The wrists, knees, and fingers were greatly swollen, and his arms terribly wasted. His heart was greatly enlarged, the liver reached the umbilicus, and there was ascites. In December 1903, he was still living, but later inquiries failed to bring any reply, and there is little doubt that he must have died. This was a most unusual case, and possibly not rheumatic. In some respects it resembled Still's syndrome, and in others "rheumatoid arthritis." There was, nevertheless, no scientific objection to the explanation of all the symptoms as those of intractable rheumatism. Such a case has clearly strong bearing upon the whole problem of the relation of rheumatism to rheumatoid arthritis.

Summary: Repeated arthritis periarticular in type; heart disease; emaciation; enlarged glands and spleen.

CASE 9. June 1901. Male, aged $4\frac{11}{12}$ years. The illness had commenced a week before with tired feelings and pain in the limbs, followed by diarrhœa and sickness. There was a history of rheumatic fever in the father's family. He was very ill and pale. His throat was reddened, and there was arthritis of both knees. The heart was dilated, and a systolic mitral murmur was audible, and was conducted into the left axilla. Five days later he developed acute pericarditis and pneumonia and died in three days. The post-mortem showed arthritis, early pericarditis, mitral endocarditis, a large spleen, and broncho-pneumonia. The diplococcus was isolated from the pericardial, cerebro-spinal, pleural, and arthritic exudations. This case died in three weeks.

Summary: Sore throat; anæmia; carditis; broncho-pneumonia; death.

CASE 10. October 1901. H. C., female, aged $4\frac{9}{12}$ years. Fourteen days before she had a sore throat, followed by multiple arthritis and heart disease. This child died in December of heart disease.

Summary: Sore throat; carditis; arthritis; death.

CASE 11. December 1901. G. P., male, aged 4 years. The mother had rheumatic fever. The child was brought for heart disease. There was advanced mitral disease, and none of the

ordinary evidences of congenital heart disease; on the other hand we could find no other proof of rheumatism. This case was lost sight of.

Summary: Heart disease.

CASE 12. January 1902. A. H., female, aged 10 months. The father had rheumatic fever. At eight months she developed chorea. When seen, she had general chorea of moderate severity. The heart was dilated, and there was a soft systolic mitral murmur. This case ran a favourable course. The chorea disappeared in four weeks, and the dilatation of the heart recovered, the murmur disappearing. At no time was there arthritis.

Summary: Chorea; cardiac dilatation; recovery.

CASE 13. February 1902. G. S., female, aged $4\frac{7}{12}$ years. Four months before coming under observation she had suffered from multiple arthritis, and an illness which the doctor in attendance called rheumatic fever. The arthritis subsided in all joints but the knees, which remained obstinate and full of fluid. Her heart was dilated, and the first sound short and feeble. Energetic treatment with salicylates had failed and contractures were commencing. On stopping all salicylates, feeding abundantly and giving quinine, there was steady improvement. The irregular fever present subsided, and in three months there was complete recovery. During this period a small firm nodule appeared on the lower end of the left radius. In June 1902, there was slight chorea. In September another nodule appeared at the lower end of the left radius. In January 1903, further nodules of the same firm, indolent character appeared over the right carpus. In January 1903, they had all disappeared, and there was apparently complete recovery. There were several unusual features about this case, and in particular the failure of the knee-joints to respond to vigorous salicylate treatment. Some will maintain that this is a proof that the condition was not rheumatic, a view we cannot accept, believing the specific action of the salicylates to be greatly overrated, and holding that the occurrence of chorea is a more trustworthy test of rheumatism. The nodules resembled those that are sometimes met with in the rheumatoid arthritis of adults. This case is again of particular interest as bearing upon our conception of rheumatoid arthritis. Some, in fact most, authorities, draw a

rigid line between rheumatism and rheumatoid arthritis, an attitude which we venture to think is not supported either by scientific investigation or by clinical experience.

Summary : Multiple arthritis ; cardiac dilatation ; nodules ; chorea ; recovery.

CASE 14. March 1902. P. C., female, aged 5 years. After two weeks of pains in the limbs, she came under observation with arthritis of both knee-joints and rheumatic broncho-pneumonia. Her heart was damaged ; there were dilatation, early mitral endocarditis and pericarditis. She recovered with mitral disease after a long illness. In 1904 there was another attack of rheumatism. This child is still under observation.

Summary : Heart disease ; arthritis.

CASE 15. June 1902. A. T., female, aged 2 years. The father and a maternal uncle had had rheumatic fever, the latter dying of the disease. The child had been ill for three months with arthritis and heart disease. There was advanced heart disease, and a nodule was present on the right olecranon process. This child had a very severe illness, but ultimately recovered with a damaged heart, only to relapse in the following August.

Summary : Carditis ; arthritis ; nodules ; lost sight of.

CASE 16. October 1902. B. J., male, aged $4\frac{1}{2}$ years. This child, living in a damp house, was brought for chorea and early mitral endocarditis. He recovered with a mitral lesion.

Summary : Chorea ; morbus cordis ; recovery.

CASE 17. January 1903. W. R., female, aged $4\frac{9}{12}$ years. The mother had had three attacks of rheumatic fever and her heart was damaged. Three weeks previously the patient had a sore throat followed by fever and pains in the limbs. The knees and elbows were swollen and stiff. The heart was not certainly damaged. Recovery followed the use of salicylates.

Summary : Sore throat ; arthritis ; recovery.

CASE 18. May 1903. F. C., male, aged $3\frac{3}{12}$ years. She had chorea, followed by heart disease, the illness commencing fourteen days before coming under observation. There were relapses in October 1904, and May 1905. The heart showed permanent mitral damage.

Summary : Chorea ; heart disease ; partial recovery.

CASE 19. May 1903. F. H., male, aged 4 years. The father had had rheumatic fever twice. There was a history

of arthritis at three years. The recent illness had lasted three months. There were arthritis, profound anæmia, carditis, and nodules. Death occurred in June from hæmorrhagic pericarditis. The diplococcus was isolated from the pericardial exudation.

Summary : Arthritis ; carditis ; nodules ; anæmia ; death.

CASE 20. June 1903. E. C., female, aged $4\frac{6}{12}$ years. She had chorea at 3, arthritis at $3\frac{1}{2}$. She came under observation for active mitral endocarditis. The temperature was raised. This patient made a slow recovery with a mitral lesion.

Summary : Acute endocarditis ; previous history of chorea and arthritis ; recovery.

CASE 21. June 1903. H. T., female, aged $3\frac{11}{12}$ years. Four weeks previously there had been multiple arthritis, and this was followed by severe carditis and chorea. This case made a slow and incomplete recovery.

Summary : Arthritis ; carditis ; chorea ; partial recovery.

CASE 22. June 1903. P. C., male, aged $4\frac{9}{12}$ years. At $3\frac{9}{12}$ years there had been a previous attack of rheumatic fever. The present illness commenced with multiple arthritis, and was followed by severe carditis, which proved fatal at the end of June. The necropsy showed adherent pericardium, mitral tricuspid and aortic endocarditis.

Summary : Arthritis ; carditis ; death.

CASE 23. November 1903. H. S., male, aged 5 years. One sister had suffered from rheumatic fever. The patient had been ill a year, first with sore throat, then with pains in the limbs, anæmia, and shortness of breath. These latter symptoms were present when first she came under observation. Recovery followed with an organic mitral lesion.

Summary : Anæmia ; heart disease ; partial recovery.

CASE 24. February 1904. A. B., male, aged $2\frac{6}{12}$ years. His sister was under observation with rheumatism. The child himself was brought for pains in the limbs and night terrors. There was no definite heart disease. This case made a good recovery.

Summary : Night terrors ; arthritic pains ; recovery.

CASE 25. May 1904. E. W., male, aged $3\frac{9}{12}$ years. When $3\frac{4}{12}$ years he had an attack of multiple arthritis. This was a very fine boy, the son of a fireman, and in this the second attack his heart was greatly damaged. The parents lived at the fire-station, the ground floor of which was always wet and

damp. The boy had further attacks in 1905, 1906, and 1907. A prominent feature was the repeated appearance of a rheumatic erythema. He is still under observation, with a greatly damaged heart.

Summary: Arthritis; erythema; carditis; anæmia; very partial recovery.

Case 26. February 1904. H. M., male, aged $4\frac{3}{12}$ years. He had had chorea for some weeks, and there was a history of a previous attack a year before. This patient had general chorea and cardiac dilatation. He made a good recovery.

Summary: Chorea; cardiac dilatation; recovery.

Case 27. May 1904. D. J., female, aged $3\frac{10}{12}$ years. The illness commenced with a slight sore throat, followed by irregular fever, multiple arthritis, anæmia, and carditis. Death occurred in August.

Summary: Sore throat; carditis; arthritis; anæmia; result, death.

Case 28. August 1904. G. O., male, aged $4\frac{6}{12}$ years. The father had had rheumatic fever. The onset of the illness was gradual with pains in the chest, breathlessness, and syncopal attacks. The heart was enormous, and there was a loud mitral murmur.

Summary: Carditis; lost sight of.

Case 29. August 1904. G. S., female, aged $4\frac{10}{12}$ years. She was said to have had rheumatism at $2\frac{4}{12}$ years. The mother had rheumatism, the father rheumatic gout. One brother had rheumatic fever three times. One sister had muscular rheumatism. The patient was brought very ill with arthritis, carditis and anæmia, nodules and chorea. He made a very imperfect recovery.

Summary: arthritis; carditis; anæmia; chorea; nodules; result, partial recovery.

Case 30. January 1905. R. B., female, aged $2\frac{9}{12}$ years. A history of seven days "cold," followed by chorea was given. The movements were general and curiously jerking and extensive, with marked facial involvement. The heart was dilated, and there was a loud systolic mitral murmur. The child did well, but since that date has had several relapses, and at the present time (1907) there is definite mitral stenosis.

Summary: Chorea; morbus cordis; recovery with mitral stenosis.

CASE 31. January 1905. W. C., male, aged $4\frac{3}{12}$ years. His illness had commenced some months previously with "a sprained ankle and wrist." For two months there had been chorea, and there was also definite cardiac dilatation and mitral disease. Recovery was uneventful, but with an organic mitral lesion.

Summary : Arthritis ; chorea ; heart disease ; recovery.

CASE 32. September 1904. A. C., female, aged 4 years. A brother was under observation with rheumatic fever. Three weeks' history of arthritis, anæmia, and shortness of breath was given. There was cardiac dilatation with mitral disease. Recovery followed with repeated relapses up to the present date (1907). There was organic mitral disease.

Summary : Arthritis ; anæmia ; cardiac disease ; imperfect recovery.

CASE 33. September 1904. W. S., female, aged $4\frac{1}{12}$ years. She had chorea for ten days. There was no obvious cardiac disease. Recovery followed.

Summary : Chorea ; recovery.

CASE 34. December, 1904. L. T., male, aged 4 years. There was ten days' history of aching pains in the legs and refusal to walk. Fainting attacks were present. There was fever and the heart was dilated. Later a mitral lesion developed. Recovery, with organic heart disease followed.

Summary : Arthritic pains ; morbus cordis ; recovery.

CASE 35. March 1905. R. W., female, aged $4\frac{6}{12}$ years. Six weeks previously she had had a sore throat followed by multiple arthritis, nodules, and carditis. Death occurred in April, when, in addition, mediastinitis, perihepatitis, and perisplenitis were found to be present.

Summary : Sore throat ; carditis ; arthritis ; mediastinitis ; nodules ; perisplenitis ; perihepatitis ; result, death.

CASE 36. May 1905. E. N., female, aged $3\frac{6}{12}$ years. The father had had rheumatic fever. A paternal aunt had had fatal rheumatic fever. Four weeks previously, after some days of malaise, with pains in the feet and many other joints, definite arthritis developed in the hands and ankles. There was much sour perspiration. Later, pericarditis, endocarditis, arthritis, nodules, and anæmia were present, and death occurred early in June. There was no post-mortem examination.

Summary : Pericarditis ; endocarditis ; arthritis ; anæmia ; nodules ; sweating ; result, death.

CASE 37. September 1905. M. A., female, aged 4. A three-weeks' history of chorea was followed by mitral heart disease.

Summary : Chorea ; heart disease ; recovery.

CASE 38. November 1905. B. S., female, aged $4\frac{11}{12}$ years. The parents had just gone into a new house. Fourteen days previously she had complained of pain in the head and " aches " in the limbs, together with a sore throat. Three days later chorea commenced. There were in addition mitral disease, fever, and cardiac dilatation. After a long illness she recovered with a much damaged heart.

Summary : Sore throat ; arthritis ; chorea ; heart disease ; partial recovery.

CASE 39. January 1906. W. C., male, aged $4\frac{3}{12}$ years. Three months previously he had suffered from " a sprained wrist and ankle." A month later chorea developed, hemiplegic in type with aphasia. There was slight dilatation of the heart ; a good recovery followed.

Summary : Arthritis ; chorea ; cardiac dilatation ; good recovery.

CASE 40. February 1906. H. F., male, aged $1\frac{10}{12}$ years. This was not a clear case, but very suggestive. His father had suffered from rheumatic fever. The child, a weakly infant, had suffered for two months from swelling of the hands. His heart was greatly damaged, with all the characters of a mitral lesion, viz. mitral regurgitation, with much hypertrophy and dilatation. There was no cyanosis or clubbing. He was lost sight of.

Summary : Arthritis ; heart disease.

CASE 41. June 1906. C. K., female, $1\frac{1}{2}$ years. A brother was under observation with active cardiac rheumatism. The child was taken suddenly ill with fever and a stiff neck, but there was neither arthritis nor heart disease. Recovery under salicylate treatment in seven days.

Summary : Stiff-neck ; fever ; recovery.

CASE 42. September 1906. S. P., female, aged 3 years. The illness began suddenly with multiple arthritis, high fever, and much sweating. The heart was dilated. A good recovery followed under salicylate treatment.

Summary : Arthritis ; cardiac dilatation ; fever ; sweating ; recovery.

CASE 43. September 1906. M. W., female, aged $4\frac{5}{12}$ years. Fourteen days before coming under observation she had a sore throat, followed by multiple arthritis, general pericarditis and mitral disease, anæmia, and wasting. Slow and imperfect recovery followed.

Summary: Sore throat; arthritis; carditis; anæmia; imperfect recovery.

CASE 44. September 1906. E. E., female, aged $4\frac{10}{12}$ years. The mother had had rheumatic fever twice. This child had, eight months previously, suffered from an attack of rheumatic fever. The second illness had commenced three weeks before with slight pain in the chest, but no dyspnœa. There was general pericarditis. This case made an excellent recovery, with a slight mitral lesion.

Summary: Carditis; recovery.

CASE 45. October 1906. W. B., female, aged $4\frac{3}{12}$ years. The family were living in a damp house in the north of London. The mother had suffered from "gout," the father from "rheumatic fever," and one sister, aged eight, from pains in the joints. The patient had been ailing for six months. There had been wasting, anæmia, and nocturnal pains in the joints. Her heart was much damaged, the mitral valve incompetent, and the cavities dilated. This case was lost sight of.

Summary: Anæmia; arthritis; wasting; endocarditis.

CASE 46. November 1906. A. W., female, aged $4\frac{6}{12}$ years. She had had three days' illness with arthritis of the wrists and ankles. In addition, there was purpura over the buttocks, legs, and thighs, and the heart was dilated. Recovery occurred under treatment by rest and salicylates. She was not seen again.

Summary: Arthritis; purpura; cardiac dilatation.

CASE 47. January 1907. H. D., female, aged 3 years. When $2\frac{1}{2}$ years this child had had an illness, in which the knees and ankles were swollen. Two months before coming under observation chorea had developed. The child was anæmic. The heart was enlarged, and there was a double mitral murmur. She made a slow recovery, and in December 1907, there was a slight relapse. Her father and paternal grandfather, and two paternal aunts, had suffered from rheumatic fever; her mother from rheumatism. The house was admittedly damp, with water in the cellars.

Summary: Chorea; anæmia; heart disease; partial recovery.

CASE 48. May 1907. L. S., female, aged $3\frac{7}{12}$ years. Two weeks after tonsillotomy she complained of pains in the limbs, and became anæmic. When first seen there was a nodule over the occiput, and the heart was severely damaged. After treatment she recovered with a mitral lesion.

Summary: Anæmia; arthritis; morbus cordis; nodule; partial recovery.

CASE 49. September 1907. F. A., female, aged $4\frac{6}{12}$ years. The family went into a damp house two months before and the father developed rheumatism in the joints. The patient complained of pains in the legs, arms, and abdomen. There was fever, and she had an excited action of the heart. Later, a mitral murmur developed.

Summary: Arthritic pains; fever; morbus cordis; partial recovery.

CASE 50. November 1907. H. C., male, aged $4\frac{8}{12}$ years. He had chorea for a fortnight. The movements were general. Speech was considerably affected. The heart was rapid; the first sound at the apex was blurred; the temperature was raised. He is still under treatment.

Summary: Chorea; early heart disease; fever.

CASE 51. December 1907. G. O., male, aged $4\frac{8}{12}$ years, subject to sore throats. The father has rheumatism. One sister had rheumatic fever. The patient four weeks before complained of pains in the left knee. Arthritis of both knees, fever, and dilatation of the heart were found. The urine contained albumin. He is still under observation.

Summary: Arthritis; fever; cardiac dilatation; albuminuria.

CASE 52. December 1907. E. S., male, aged $4\frac{10}{12}$ years. The father and brother have rheumatism. Pains in ankles and knees for some weeks, followed by chorea of moderate severity were complained of. Now there was definite chorea and mitral heart disease. He is now under observation.

Summary: Arthritis; chorea; morbus cordis.

In this series the frequency of the association of rheumatism with damp houses is noteworthy, as also the strong family history of the disease in many instances.

Appendix II

Seventeen cases of rheumatism in children over five years, in which there was a history of a previous attack before the fifth year

1. S. A., female, aged 6. Repeated attacks and severe cardiac damage. Arthritis at 15 months.

2. F. P., male, aged 7. Chorea. Arthritis at $2\frac{1}{2}$ years.

3. B. F., female, aged 10. Severe morbus cordis of old standing. Muscular rheumatism at $1\frac{6}{12}$ years.

4. C. B., male, aged $5\frac{5}{12}$. Severe rheumatism and heart disease. Rheumatism at 3 years.

5. S. B., female, aged 6. Purpura. Arthritis and dilated heart. Rheumatism at 3 years.

6. L. D., male, aged 6. Rheumatic heart disease. Arthritis at 4 years.

7. L. B., male, aged $5\frac{3}{12}$. Severe rheumatic heart disease. Rheumatism at $4\frac{6}{12}$ years.

8. J. S., aged $6\frac{1}{12}$. Severe rheumatic heart disease. Rheumatic fever at 3 years.

9. J. R., female, aged 6. Severe heart disease. Acute rheumatism between 4 and 5 years.

10. H. K., male, aged $5\frac{9}{12}$. Fatal rheumatic fever. First attack at 4 years of age.

11. J. B., male, aged 7. Morbus cordis. Rheumatism at 3 and 5 years.

12. L. R., female, aged 6. Advanced heart disease. Arthritis at 15 months.

13. E. P., female, aged 6. Chorea and heart disease. Chorea at 4 years.

14. J. W., male, aged 11. Fatal rheumatic fever. Rheumatic fever at 3 years.

15. F. W., female, aged $8\frac{1}{2}$. Rheumatic arthritis and heart disease. First attack at 4 years.

16. C. C., male, aged 9. Rheumatic heart disease and nodules. Articular rheumatism between 4 and 5 years.

17. F. C., female, aged 8. Chorea and morbus cordis. Articular rheumatism at 4 years.

PAPER NO. XXII

A CONTRIBUTION TO THE STUDY OF RHEUMATISM, WITH NOTES ON THE AFTER HISTORY OF TWENTY-FIVE CASES OF "SCARLATINAL RHEUMATISM"

(Reprinted from the *Quarterly Journal of Medicine*, October 1909)

In this clinical paper the histories of cases of "rheumatism" arising in direct association with scarlet fever have been traced over some years, and it is shown that the examples described are indistinguishable from cases of acute rheumatism arising independently of the disease. The explanation is put forward that the rheumatic infection invades the system in association with the "sore throat" of the exanthem. The possibility of throwing light upon the problem of the streptococci by a comparative study of the rheumatic diplococcus and the streptococcus described by Dr. Mervyn Gordon is commented upon.

SCARLATINAL rheumatism is of special interest because of its comparative frequency in this country, and because we have on one hand the researches of Mervyn Gordon and others on the streptococcus that occurs in scarlet fever, and on the other the investigations that have been made upon the same family of bacteria in acute rheumatism uncomplicated by scarlet fever. Further, in both scarlet fever and rheumatism the importance of sore throat is generally recognised, and lastly, whatever the true explanation of scarlet fever itself may be, we may reasonably look upon it as likely to influence any concomitant rheumatic infection.

In looking through the first volumes of the post-mortem records of the Hospital for Sick Children, Great Ormond Street, which date back some fifty years, it is interesting to find ourselves in the days when cases of scarlet fever were admitted and were often extremely virulent. It would have been still more interesting if cultures had been made in those days from

the fatal cases of pericarditis, for then a description of any micrococcus which had been isolated might have been compared now with that which has been since isolated from uncomplicated rheumatic pericarditis. Fortunately, the researches of Gordon enable us to get a clear idea of the streptococcus which he isolated from cases of severe scarlet fever and which has some points of close resemblance to the rheumatic micrococcus.

Clinical investigation has proved the occurrence of multiple arthritis, chorea, nodules, heart disease, sore throat, purpura, erythemata, and psoriasis, in association with true rheumatism and scarlatinal rheumatism, and in this contribution the after histories of 25 cases of rheumatism in childhood directly associated with scarlet fever have been traced during the last eight years. These children have come for symptoms of rheumatism, and, so far as can be observed the clinical features are identical with those of acute rheumatism. One case was fatal (No. VI) from pericarditis, and a strepto-diplococcus was isolated, which, working along the lines we had pursued in other cases, showed the same characters as the diplococcus of rheumatism. It was minute, strongly acid-producing diplococcal in the fibrinous exudation, and on experiment caused multiple arthritis and heart disease in rabbits with no suppuration in the viscera. The virulence was soon lost, but the growth once established was persistent in subculture.

It will be seen from the recorded cases that the children who suffered from rheumatism during scarlet fever were liable to relapses in which multiple arthritis or chorea or morbus cordis might light up again, and several of these symptoms might appear together. The arthritis was benefited by salicylates, the chorea ran the same tedious course, the cardiac lesions were chiefly mitral and showed no peculiarities, except perhaps a greater tendency to tachycardia.

Scarlatinal rheumatism is well known to commence either soon after the initial sore throat or, as these cases show, in association with a secondary sore throat, and this reminds us that the portal of entrance of the rheumatic organism which has been the most certainly proved is the tonsils. It may be mentioned in passing that among the many cases of acute rheumatism in childhood, recorded in our hospital notebooks, we find that the two other acute infections from which parents

have specially dated attacks of rheumatism in their children have been measles and diphtheria, and both these are associated with sore throats. These personal investigations have been made quite independently of the views of other observers, but when they are compared with the statements that have been made in the standard article on scarlet fever by Dr. Caiger in Allbutt and Rolleston's "System of Medicine," it is apparent that he, writing from his aspect of scarlatinal rheumatism, approaches towards the same position as the one to which we incline. Thus he writes: "There are good reasons why it should be regarded as pathologically akin to ordinary acute rheumatism, though differing in certain respects. It is very prone to arise in persons who have been subject to attacks of acute rheumatism, although such subjects are in the minority. It shows, though in a less degree, the same tendency to move from joint to joint, and it is readily amenable in most instances to the action of salicylates. On the other hand, it is less severe than ordinary acute rheumatism, its natural bent being towards recovery: it is unattended with the acid perspirations and the creamy furred tongue so characteristic of that condition, and it is less prone to affect the tissues of the heart and pericardium. Moreover, the joints are more prone to take on a suppurative action leading to a condition of pyæmia than in ordinary rheumatism."

Dr. Caiger is naturally presenting the subject of scarlatinal rheumatism from a somewhat different point of view, for he is writing of scarlet fever irrespective of the age of the patients, and from observations during the course of the acute attack. On the other hand, we are only concerned with children under 12 years of age who have recovered from the scarlet fever, and we have seen the rheumatism when uncomplicated by its presence. Yet each of us, in common with many others, are struck by the close resemblance of true and scarlatinal rheumatism, and *we believe that it is in many cases true acute rheumatism.* Later in his observations Caiger adds that scarlatinal rheumatism is far more common in adults than in children, and that the cardiac structures are rarely involved at the time, probably in less than three per cent. These observations, if it were not for the saving clause as to the relative frequency in adult life, would be strong evidence against the true rheumatic origin of scarlatinal rheumatism. The saving clause reminds

us that valvular and pericarditic disease are less frequent in adult than in child life.

Our cases show clearly enough that heart disease is a common event in childhood after scarlatinal rheumatism. Thus 16 out of 25 had obvious organic valvular disease, and several of the remainder had dilated hearts or suspiciously feeble first sounds. Sour sweats, we know, are not a feature of rheumatism in childhood.

We must next make a brief reference to a discussion on rheumatism and its allies in children, introduced by Sir Thomas Barlow at the annual meeting of the British Medical Association held at Liverpool in 1883. This is to look back over a quarter of a century! On the subject of scarlatinal rheumatism Sir Thomas Barlow thus sums up: "It seems possible that there may be at least two different forms, but at all events with regard to many of the cases occurring during convalescence, and with regard to the mild relapsing cases occurring towards the end of the first week, we must consider that if not identical they are indistinguishable from true rheumatism." Dr. Ashby, in the discussion, described two cases in which pus was found in the joints and strongly lent to the pyæmic nature of this complication. To quote his words: "In the first place, there is the greater frequency of occurrence in some outbreaks than in others. Secondly, the regularity with which the joint affection supervenes at the end of the first week; thirdly, the severity of the scarlatinal symptoms and the lightness of the joint affection in most cases, and the suppuration which took place in two of the cases; and lastly, the absence of serious heart affections." We may well wonder if to-day we have advanced a single step from the position of 1883. We believe, however, that the bacteriological investigations on scarlet fever and acute rheumatism have really brought us a little nearer to the means of closer investigation, and to a more complete understanding of the problem.

The clinical and pathological facts in our series seem to point irresistibly to the occurrence of true acute rheumatism in scarlet fever, although there is the other problem to be borne in mind, the possibility that there may also be a form of rheumatism peculiar to scarlet fever. This we are not in a position to affirm or deny, but we feel that if it exists it has not yet been clearly delimited from the true rheumatism, and

we must bear in mind the possibility of a modifying influence on true rheumatism due to the scarlatinal poisoning. The bacteriological problem is a most difficult one, and it would be a great assistance if a careful investigation could be made by an independent observer of the micrococcus isolated by Gordon from scarlet fever and that obtained by ourselves and others from acute rheumatism. We use the term "independent" because it has repeatedly struck us that laboratory investigations on the streptococci are carried on by different methods, along different lines and with different standards by the various workers, and each one has a tendency to lay stress on some particular test or tests which he considers more or less specific. Dr. Vernon Shaw was able to prove to his satisfaction by the tests that he applied that the micrococci described by Wassermann, ourselves, and Walker were identical. If some one working with virulent streptococci from scarlet fever of Gordon's type and virulent streptococci of the rheumatic type could make an unbiased comparison of them, it seems probable that we should gain another step in the study of rheumatism. That they are closely allied the researches of Gordon, Andrewes, Horder, ourselves, Walker, and Beattie have already shown. What are their specific differences when studied together and by experimental methods, and the value of these specific differences, are the essential points we require to know.

Appendix

Twenty-five cases of rheumatism directly associated with scarlet fever

Case 1. September 13, 1900. R. C., female, aged 9. When 6 years old in 1897 she had an attack of scarlet fever followed in the fifth week by "rheumatism" (viz. arthritis), which kept her in bed for some weeks. This child was brought in 1900 for a first attack of chorea with a dilated heart. In 1901 she was again brought for chorea. In 1902 for pleurodynia and endocarditis. In 1904 she had well-marked double mitral disease.

Summary: "Scarlatinal rheumatism"; chorea, pleurodynia; morbus cordis; relapsing type.

CASE 2. October 27, 1900. W. W., female, aged $7\frac{8}{12}$. Scarlet fever in December 1899. Not well since, but subject to sore throats and pains in the muscles. One sister had had rheumatic fever, another "muscular rheumatism." September 1900, severe rheumatic arthritis. October 1900, chorea, in hospital for seventeen weeks. March 1901, chronic rheumatism and chorea still continue; evidence of early mitral stenosis now apparent.

Summary: Never well since scarlet fever; sore throats; arthritis; chorea; morbus cordis.

CASE 3. M. K., female, aged 6. April 15, 1902. This patient was in a fever hospital suffering from scarlet fever and "rheumatism" for thirteen weeks. Three days after leaving hospital she relapsed with pain in her left side and dyspnœa. She had never had rheumatism before, but her mother had suffered from rheumatic fever when twelve years of age, and an elder brother also suffered from rheumatism. She was exceedingly anæmic and orthopnœic, with a temperature of 104° F., pulse of 144 and respiration 68 to the minute. Pericardial and pleuropericardial friction were present and also extensive endocarditis. Death occurred in seven days.

The necropsy showed a turbid greenish-yellow fluid with plastic exudation in the pericardial cavity. Early vegetations were present on the mitral tricuspid and aortic valves. Renal disease was present, and a small white infarct was also found in each kidney. A minute diplo-streptococcus, obeying the cultural and morphological characters of the rheumatic diplococcus, was isolated from the pericardial exudation. This produced arthritis, pericarditis, and endocarditis on intravenous injection into rabbits.

This was a case of particular interest because there was both a definite history of scarlet fever and a strong rheumatic family history. The micrococcus resembled the rheumatic diplococcus in essential characters, and the post-mortem evidence showed a condition quite indistinguishable from that found in virulent rheumatism.

Summary: Scarlet fever; "rheumatism"; virulent and fatal pericarditis. *Necropsy:* Diplo-streptococcus in pericardial exudate produced multiple arthritis, pericarditis, and endocarditis on intravenous injection into rabbits.

CASE 4. E. A., female, aged $7\frac{1}{2}$. June 18, 1902. When

4 years old had a severe attack of scarlet fever, immediately after which she complained of pain in her knee-joints, but recovered from this entirely. The following year she again had pain in her knee-joints with effusion which lasted for six months. The effusion appeared first in the left knee, then later in the right, and then again in the left. Since this second illness she had never been well. There was no personal history of rheumatic fever and no immediate family history, but her maternal grandfather suffered from rheumatic fever.

This child had great swelling of both knee-joints with much pain and muscular wasting. The left hip-joint was also painful. There was tachycardia, but no valvular disease. One enlarged lymphatic gland was felt in the right groin. The spleen was not enlarged. We explored the left knee-joint, obtaining a quantity of clear effusion, containing a few polymorphonuclear leucocytes, but no micrococci, and all cultures were sterile.

Salicylate treatment was ineffectual, and in September the condition was still most intractable, and although her general health was improved, both knee-joints presented the appearance of "rheumatoid arthritis." Most unfortunately we lost sight of her after September and must be accordingly content to record her case as one of rheumatoid type of obscure nature following scarlet fever.

Summary: Scarlet fever; "rheumatism"; chronic relapsing arthritis of the rheumatoid type; tachycardia; cultures from arthritic exudation negative.

CASE 5. A. S., female, aged 10. November 26, 1902. At five years of age was thirteen weeks in a fever hospital suffering from scarlet fever followed by chorea. Three years later was admitted to a London hospital for "rheumatism in her joints." Following the scarlet fever psoriasis developed and relapses occurred each year (five times) accompanied by pains in her limbs. She came under observation for a second attack of chorea together with psoriasis. Her heart was dilated and there was an occasional soft mitral murmur. This attack of chorea ran the usual course.

Summary: Scarlet fever; chorea (two attacks); arthritis; psoriasis (five attacks).

CASE 6. C. W., female, age not stated. March 7, 1903. Six months previously had an attack of scarlet fever followed

by "rheumatism." During the scarlet fever her throat was very inflamed. This child had recovered from the arthritis, but was brought six months later for a severe attack of chorea, accompanied by dilatation of the heart and arthritis pains.

Summary: Scarlet fever; "rheumatism"; chorea; arthritic pains; cardiac dilatation.

CASE 7. W. S., male, aged 6. October 1903. In June 1903, was ill for two months with scarlet fever. Three weeks later developed a sore throat followed by rheumatism for which he was detained five weeks in a London general hospital. In September, a week after leaving, he developed erythema multiforme, a sore throat, and shortness of breath. We found him suffering from severe mitral disease and bronchitis, and so far as we could ascertain this heart disease showed no characters by which it could be distinguished from ordinary rheumatic heart disease.

This case may be looked upon as an example of acute rheumatism which chanced to happen after an attack of scarlet fever, but the sequence of events is so close as to make it worthy of record when considering the wider question of scarlatinal rheumatism.

CASE 8. V. W., female, aged 6. November 4, 1903. This child had an attack of scarlet fever at two years (in 1899), and ever since had been in poor health and suffered from shortness of breath owing to a damaged heart. She came under observation suffering from chorea with well-marked mitral disease and hypertrophy of the heart. The chorea was chiefly on the right side with much speech defect. In January 1904 she had recovered from the chorea, but remained in the same condition as regards her heart.

Summary: Scarlet fever; morbus cordis; chorea.

CASE 9. G. F., male, aged 10. August 10, 1904. Scarlet fever at the age of 7 and at that time arthritis of the ankle-joints. At the age of 9 multiple rheumatic arthritis with heart disease. Brought in 1904 for a third attack of arthritis with tachycardia and a cardiac murmur. This boy improved under salicylate treatment. In April 1905 he again relapsed with arthritis and cardiac disease.

Summary: Scarlet fever; arthritis (repeated); tachycardia; morbus cordis.

Case 10. W. H., male, aged 10. April 1, 1905. Quite well until scarlet fever at the age of 6 years in 1901; he was then in a fever hospital for three months suffering from "rheumatism." On returning home he developed chorea. This boy came suffering from a second attack of chorea with well-marked mitral disease, the condition being, so far as could be determined, indistinguishable from the chorea and morbus cordis of acute rheumatism.

Summary: Scarlet fever; arthritis; chorea (two attacks); morbus cordis.

Case 11. A. A., female, aged 9. April 8, 1905. The mother of this child suffered from chronic rheumatism, and the patient herself, three months before coming under observation, suffered from an attack of multiple arthritis in the fourth week of scarlet fever. She was brought for rheumatism in the limbs, dilatation of the heart, and slight chorea. Her illness ran an ordinary course.

Summary: Scarlet fever; arthritis; chorea; cardiac dilatation.

Case 12. M. O., female, aged $9\frac{1}{2}$. May 15, 1905. This case presents the relation of scarlet fever and rheumatism from a somewhat different point of view. The patient had suffered from rheumatic fever when 6 years of age, and two years later from an attack of scarlet fever in which occurred multiple arthritis, affecting the wrists and knees. She came about eighteen months later with chorea and well-marked mitral disease. Her illness showed no unusual features. This case, as do several others in this series, exemplified the point that Dr. Caiger emphasises in his article on scarlet fever in Allbutt and Rolleston's "System of Medicine," *i.e.*, the occurrence of scarlatinal rheumatism in those who are rheumatic in constitution.

Summary: Acute rheumatism; later scarlet fever and arthritis; later chorea and morbus cordis.

Case 13. W. H., male, aged 10. June 17, 1905. Four years before coming under observation in 1901, he had an attack of scarlet fever followed at once by chorea. There was no family history of rheumatism. This boy had come to the hospital for an attack of rheumatism of three months' duration, commencing with arthritis and chorea. He had well-marked mitral disease with considerable dilatation. The condition was

characteristic of ordinary acute rheumatism and recovered in the usual imperfect manner. In November 1906 he suffered from epistaxis and again came back with a dilated heart, œdema, and severe mitral disease.

Summary: Scarlet fever; chorea (two attacks); arthritis; morbus cordis.

CASE 14. F. S., female, aged 11½. October 28, 1905. Three years before (in 1902) she had an attack of scarlet fever followed by chorea three months later. During the scarlet fever there was "rheumatism" in the joints. A year later there was a second attack of chorea. This patient came with a history of pains in the ankles and knees of 14 days' duration with mitral disease and violent chorea which ran a protracted course.

Summary: Scarlet fever; arthritis; chorea (three attacks); morbus cordis.

CASE 15. K. R., female, aged 7 4/12. February 1906. This case is of interest for its bearing upon the rheumatism of scarlet fever. Her sister was suffering from rheumatic heart disease and chorea. The child herself had suffered from scarlet fever with severe angina, and had left the hospital three weeks. During those three weeks she was noticed to be exceedingly nervous and could not be left alone at night. She also complained of headaches. Then she became fidgety and came to the hospital with obvious chorea and cardiac dilatation. The chorea became severe, but she eventually recovered with apparently no permanent cardiac lesion. In January 1908 she again came with a relapse of chorea associated with a sore throat.

Summary: Scarlet fever; chorea (two attacks); cardiac dilatation.

CASE 16. M. W., female, aged 6. October 27, 1905. This case again illustrates the close association of acute rheumatism and scarlet fever. The mother of the child suffered from "rheumatism" and the patient in April 1908 was nine weeks in a fever hospital suffering from scarlet fever, during which illness she developed multiple arthritis. Immediately on her return home she developed chorea. The patient came for shortness of breath and pain in the chest, and had a characteristic early mitral lesion.

Summary: Scarlet fever; arthritis; chorea; morbus cordis.

CASE 17. B. C., male, aged 7. November 10, 1906. Two years before had an attack of scarlet fever with nephritis, and heart disease. He came suffering from a double mitral lesion with general cardiac enlargement and no renal affection.

It is not unreasonable to suggest the cardiac lesion was rheumatic, and possibly also the nephritis. It can be safely asserted that the condition of the heart did not resemble that which we usually recognise as a sequela of chronic renal disease in childhood. The high pulse tension, slightly thickened vessels, and hypertrophied left ventricle of such cases were not present, but there was a condition resembling the usual double mitral disease of acute rheumatism.

Summary: Scarlet fever; mitral disease; nephritis.

CASE 18. L. M., female, aged 8. June 12, 1907. The mother of the patient had suffered from rheumatic fever. The child herself had an attack of scarlet fever in February 1907, and at the end of March developed chorea, for which she came to the hospital. Her recovery was good and without an apparent cardiac lesion.

Summary: Scarlet fever; chorea.

CASE 19. E. N., aged 7. February 22, 1908. When five years old had an attack of scarlet fever with nephritis and arthritis in the hands. Since that time has had rheumatic pains. Brought with morbus cordis. The heart was enlarged; there was a systolic mitral and a slight presystolic murmur.

Summary: Scarlet fever; arthritis; nephritis; morbus cordis.

CASE 20. G. B., male, aged $10\frac{1}{12}$. April 1908. The maternal uncle of the patient had suffered from rheumatic fever; his mother from "rheumatics." This child had an attack of scarlet fever in September 1907, and had a relapse of sore throat followed by rheumatism in the joints; hands, wrists, and elbows being affected. In November, after recovery from the "rheumatism," he developed chorea. Brought April 10, 1908, for a relapse of chorea.

Summary: Scarlet fever; arthritis; chorea (two attacks).

CASE 21. L. T., female, aged 10. April 15, 1908. Some years previously had an attack of scarlet fever, followed at once by rheumatism in the joints. Since that time short of breath and subject to fainting attacks. This case was of interest, because there was persistent tachycardia (pulse 120), some general enlargement of the heart, and a faint mitral

murmur. The urine was not albuminous. It appeared to be a case in which myocardial disease was the prominent feature, and the balance of evidence favoured the view that it was rheumatic in nature.

Summary: Scarlet fever; arthritis; morbus cordis.

CASE 22. W. P., male, aged 6½. August 8, 1908. Scarlet fever a month ago. Brought for a sore throat. Anæmia; abdominal pain and pains in the wrist. Examination showed active heart disease with a temperature of 101.4°. This case ran a very severe protracted course, lying for many weeks in the hospital with active heart disease. In December 1908, shortly after leaving the convalescent home, he returned very ill with a greatly damaged heart, rheumatic nodules over both elbows, and vague muscular and articular pains.

This case can perhaps hardly be claimed as an example of "scarlatinal rheumatism," but rather as one of malignant rheumatism following scarlet fever. It is worth recording in the series, because though a month elapsed after the scarlet fever before the boy was brought, it is certain that the condition had been in existence for some days, and possibly a week or more, which would date its onset very close to the fever.

Summary: Scarlet fever; morbus cordis; arthritic pains; anæmia; nodules.

CASE 23. W. K., female, aged 7. September 19, 1908. Scarlet fever and rheumatism in May 1908. In September a return of the pains in the limbs with fever and sore throat. Early mitral disease. Her mother had suffered from rheumatic fever.

Summary: Scarlet fever and "rheumatism." Later, sore throat; rheumatic pains; morbus cordis.

CASE 24. C. C., female, aged 8. September 19, 1908. This child had previously been under observation, suffering from rheumatic morbus cordis. She now developed scarlet fever, and in October immediately after the attack of fever was over, she became choreic.

Summary: Rheumatic fever; morbus cordis; scarlet fever; chorea.

CASE 25. C. T., male, aged 9. November 11, 1908. Ten weeks before coming under observation had suffered from scarlet fever, during which there were rheumatic pains. Immediately on leaving he was noted to begin twitching.

There was obvious chorea, anæmia, albuminuria, but no obvious cardiac murmur. His father suffered from rheumatism.

Summary : Scarlet fever ; chorea ; albuminuria.

An interesting point becomes apparent from a study of this series, viz., that one symptom of rheumatism may be noted while a child is in a fever hospital, which may quiet down under treatment. When, however, the child leaves there frequently appears within a month from departure another symptom of rheumatism (chorea in particular), showing that the disease was only apparently cured in the fever hospital. This has important bearing upon the ultimate prognosis of scarlatinal rheumatism.

PAPER NO. XXIII

A RESEARCH UPON COMBINED MITRAL AND AORTIC DISEASE OF RHEUMATIC ORIGIN. A CONTRIBUTION TO THE STUDY OF RHEUMATIC MALIGNANT ENDOCARDITIS

(Reprinted from the *Quarterly Journal of Medicine*, July 1912, vol. v, No. 20)

The introductory part of this paper is concerned with answering further criticisms which had been raised by various writers, and in particular the one which holds that the view that acute rheumatism is a specific disease is based upon insufficient evidence.

The chief part of this contribution is devoted to the study of combined mitral and aortic disease in rheumatism, with the object of demonstrating that in this lesion must be sought the connecting link bewteen "simple" and "malignant" rheumatic endocarditis. If this view is a correct one, it follows that the terms "infective" and "non-infective," "simple" and "malignant," as applied to endocarditis are better abandoned for the more accurate one of "active"—the nature of the infection being supplied as far as possible by the corresponding adjective: thus, active rheumatic, pneumococcic, staphylococcic, &c., endocarditis. Particular emphasis is laid upon the importance of studying endocarditis as an event resulting from an infection, that is, studying it as a symptom of disease and not as a disease in itself.

Section I

(*a*) *Object of the communication.* We return in this investigation to the consideration of the second statement that we made in our paper upon the causation of acute rheumatism published in the *Lancet* in September 1900. This statement was to the effect that *acute rheumatism produces a malignant as well as a simple endocarditis.*

At the outset we would insist upon the exact wording of this assertion in order to avoid the mistake being made that we

are thought to maintain that rheumatism is the only cause of this condition.

It has been repeatedly proved that there are many causes of malignant endocarditis, and we would venture to make the generalisation that any infection which attacks the valves of the heart may produce this lesion, and to express our belief that when an infection which only produces endocarditis exceptionally does happen to attack the valves then the malignant form of endocarditis is prone to result.

On many previous occasions we have commented upon the peculiar attitude that has been adopted to rheumatism, in that it has been almost universally taught that it is a cause of simple or healing endocarditis, but needs the assistance of a secondary infection to produce the malignant form. Surely this is a curious example of seeking a difficult path, when the plain and easy one lies before us.

In this paper we are approaching our subject from a somewhat different point of view to that from which we dealt with it in a former paper (No. XV), for we are here studying a form of heart disease which we believe every one must allow may be the result of the rheumatic infection itself and not of any added infection.

In the course of this communication we shall quote from our former paper which established certain facts that may be lawfully utilised to illustrate our present contention, which is to this effect : *That from a study of severe heart disease of rheumatic origin involving lesions to two important valves, we find all gradations between simple and malignant endocarditis, and additional and striking proof of the existence of a malignant rheumatic endocarditis.*

We would also add that the original distinction between non-infective and infective as applied to endocarditis should not be allowed to remain for that such a division is in our opinion a survival of an obsolete pathology, and as such is a hindrance to advance in the study of heart disease.

(*b*) *Acute rheumatism a specific disease.* We are desirous at this point of dealing with a criticism of our investigations which has been frequently repeated, and has been recently made again at a meeting of the Pathological Section of the Royal Society of Medicine in March 1912. It is one to this effect, that *we assume the fact that there is a specific disease, acute*

rheumatism. It is impossible for any but skilful speakers to answer such a criticism as this in a short debate, but we are prepared to put in writing the reasons for our contentions, to which we firmly adhere and by the truth or falsity of which we are prepared to stand or fall.

The question is one the answer to which necessarily brings us in contact with fundamental conceptions of human disease, and we would urge at once that diseases such as acute rheumatism are not and never will be conditions that can be pigeon-holed into compartments with rigid walls. The farthest one can see clearly concerning such a problem is this : That certain pathological processes may produce results in the human body, which, when they prove fatal, can be studied sufficiently thoroughly, sufficiently accurately, and sufficiently frequently to permit the statement that they clinically and pathologically present a process of disease unlike any other. Such a disease we hold must be built up upon the study of fatal cases, although it may be frequently delimited at the bedside when not fatal.

It is not in our opinion any scientific objection to the view that we put forward for a critic to quote a case which has been thought by many doctors to be acute rheumatism and yet has proved to be of a different nature because, for example, a staphylococcus has been isolated and the patient cured by a vaccine ! What scientific weight can such a statement as that possibly have ? We should be the first to allow that we have made and shall make errors in the clinical diagnosis of acute rheumatism, and that other diseases may resemble it very closely. We do not suppose acute rheumatism is the only cause of a transient polyarthritis in man ; or that it is the only disease that produces heart affections, or even arthritis and heart disease combined. Twelve years ago we were conversant with these cardinal difficulties in the study of acute rheumatism which from time to time are presented to us by critics as though they were new suggestions. We have, indeed, ourselves pointed out that some cases of infection that result from middle-ear disease are almost impossible to distinguish from acute rheumatism. Yet no one would attempt to study any disease by the uncertain light of exceptional cases, for such a procedure would be foredoomed to failure, and it is essential, we think, in studying acute rheumatism to investigate

the classical examples of which in our Hospital note-books there are ample records.

The first step that we have believed essential for establishing the specific nature of this disease has been to study side by side post-mortem records and clinical histories of acute rheumatism. In this way we have obtained not only the results of our own experience, but the independent observations of many different skilled physicians and pathologists. The remarkable records at the Hospital for Sick Children, Great Ormond Street, alone contain upwards of 200 fatal cases, and in addition to this we have many examples in older subjects recorded in recent years at St. Mary's Hospital and University College Hospital. Further, we have investigated microscopically on many occasions the important cardinal lesions and the exudations of the disease. Lastly, we have investigated the bacteriology in nearly 100 cases, and studied the experimental lesions.

The outcome of these investigations has been that we hold that there is decisive evidence from clinical and pathological observations of fatal cases that acute rheumatism is one of the most special of diseases in this country—a view we believe to be supported by nearly every physician of eminence who has studied in a Children's Hospital. Evidence such as this is not to be lightly set aside by the relation of unusual cases, or of cases unsupported by accurate clinical and post-mortem investigations.

It is as the infective agent of this specific disease that we claim the diplococcus, and would add that the statement made by critics that various bacteria have been isolated from cases of rheumatism should carry now no real weight. The only evidence we hold that can be now admitted as worthy of consideration is that which brings with it the proof that these various bacteria have not only been isolated, but have reproduced the lesions of the disease, as has the diplococcus. Those who maintain that the cause of the disease is still unknown should in all fairness now, after a period of at least ten years has elapsed, during which positive results have been obtained by others, justify their cause by some slight positive contribution of their own to our knowledge.

In a recent and admirable review of the study of rheumatism during the last decade by Sanderson,[1] our position and that of others who support our views has been described as becoming

more isolated. Even if we admit this—which we do not—we would venture to ask of the impartial looker-on, whether scientific inquiry is to be measured by the number of investigators or by the character of the results? As far as acute rheumatism is concerned, with the increasingly isolated group of investigators remain such results as the demonstration of experimental arthritis both acute and chronic, endocarditis simple and malignant, pericarditis, myocarditis, pleurisy, peritonitis, pneumonia, nodule formations, appendicitis, choreiform movements, large white kidney, and infarctions—all obtained by a micrococcus isolated from the cardinal lesions of acute rheumatism, and most of them previously quite unknown in the experience of pathologists in this country.

Various Types of Rheumatic Infection

If acute rheumatism is a specific disease, the result of infection with a diplococcus of the streptococcal group, what clinical types of the disease may be reasonably expected to be met with? The answer to this question has important bearing upon our investigation of a hundred cases of mitral and aortic disease of rheumatic origin, for we wish to show that this infection is not extraordinary in its behaviour but quite in accord with what may be reasonably expected of such a condition.

Firstly, it may produce a more or less general infection and damage many organs. Sometimes it does this very acutely, but more frequently with a moderate degree of severity. In this group will be found, as is the case with other infections many examples in childhood. In such, mitral and aortic disease is only one incident, and there are in our list classical examples of such cases which have proved fatal.

Secondly, the severity of the infection may fall on certain organs, notably the heart, or even upon certain parts of the heart, for example the valves.

These lesions may heal and leave scars which in the case of valvular lesions may introduce a new train of symptoms the result of mechanical heart disease. In our list there are convincing examples of this occurrence.

Again, the lesions may heal, or rather let us add appear to heal, almost entirely and yet exacerbate, or arise anew as a result of fresh activity,with the result that we find after death,

evidences of scarring and activity combined. Thus, *thirdly*, the active lesions in the valves in such cases may be only incidents in a renewed general infection, or, *fourthly*, they may, as we shall hope to show, be the cause of death by a virulence and activity which are recognised under the name of malignant endocarditis.

Fifthly, from the first the endocardial lesions may show this malignancy and be the cause of death.

Such various results of infection as these are in no way remarkable ; indeed, as we have previously stated, it would be much more remarkable if they did not occur.

Sixthly, it is only to be expected that in a long series of cases of mitral and aortic disease examples will occur which are exceedingly difficult to group.

The result is we arrive at the conclusion that as a consequence of the rheumatic infection we may find every grade, from a primary malignant endocarditis to long healed lesions, which have caused death, not from any active process but entirely from a mechanical disability of the circulatory apparatus, the result of the scarred and deformed valves.

Necessity for considering Mitral and Aortic Disease in Rheumatism as an Event in the History of an Infective Process

There are few physicians who have not been struck with the paralysing effect of nomenclature in the study of disease. We have here, we think, a very good example of such an occurrence. In looking through records it is brought home to us that a condition such as combined mitral and aortic disease of rheumatic origin is repeatedly looked upon as an example of " heart disease." We must emphasise that for our purpose such a conception is practically useless, and moreover it is frequently not correct. The condition is undoubtedly in a sense one of heart disease, and when these lesions represent the scars of some long dead infection such a description is correct, but when, as reference to our list of cases will at once make clear, there are not only valvular lesions but active valvular disease, the condition is not one of heart disease but of active heart disease ; that is, it is a phase in the life-history of a prolonged infective process. Our paper rests in great part on this study of these valvular lesions as active events in acute

rheumatism, and we shall endeavour to place them in the picture of a rheumatic infection, and not to isolate them under the benumbing title of "heart disease."

The combined lesion can be produced experimentally both as the result of a single and of a repeated infection, and in some instances the involvement of the two valves has appeared to be the result of a direct spread of the infection from one valve to the other, the segments being in very close proximity (*see frontispiece*). The usual sequence on account of the greater frequency of mitral disease is for the aortic valve to be affected the later of the two, but we would not deny the possibility of the reverse occurrence, although up to the present we have had no experimental proof in its support.

At the bedside also we find the two lesions appearing in various ways. Sometimes the aortic disease follows rapidly upon the mitral during a prolonged attack of endocarditis. Sometimes after a pause in the activity of the infection, but before the patient is well enough to leave bed, there is a definite recrudescence with the appearance of an aortic lesion. Again, aortic disease may arise in a subsequent attack, and then it is very difficult to decide whether it is an independent infection of the valve by rheumatism or whether it is that this lesion is recognised by the appearance of new clinical signs, but its origin in reality a spread from the older mitral endocarditis which has simultaneously reawakened to activity. Lastly, the aortic lesion may be the first event, although this is a less frequent occurrence.

The combination of valvular disease is of interest because it shows that in the young mitral regurgitation due to relative incompetence of an undamaged valve is decidedly rare as a result of aortic regurgitation, for in such cases there is almost invariably active disease of the mitral valve also. It is, however, of far greater interest because it suggests *the dawning of a malignant tendency in the endocarditis*. We believe also that in man, as in animals, there may be a direct spread of infection from one valve to the other, and that when this is the case we have one of the great features of the malignant type. In the post-mortem records of malignant endocarditis emphasis is invariably laid upon the spread of vegetations to the heart wall, to the chordæ tendineæ, to the musculi papillares, or the wall of the aorta. A direct spread from one

valve to another in immediate proximity in no way differs from these occurrences.

The clinical study of rheumatic mitral and aortic disease illustrates well that behaviour of the rheumatic infection in the tissues which we have already foreshadowed.

Thus, *firstly*, the valvular lesions may be but one incident in a fatal general infection, as for example in the case of a boy aged 4½ years, who died in a first attack of acute rheumatism after twelve weeks' illness. During life there were polyarthritis, nodules, and aortic and mitral disease with pericarditis. After death, subacute pericarditis was demonstrated with acute mitral and aortic endocarditis. In such cases we are dealing with acute rheumatism invading many tissues.

Secondly, the endocardial lesions may completely heal and the patient die of cardiac disabilities (asystole), aortic or mitral in type, in accord with the predominance of the particular lesion.

Thus, for example, a man aged 42, who had suffered repeatedly from acute rheumatism, came under observation for mitral and aortic disease with dyspnœa and repeated attacks of angina pectoris. There was no fever and death was sudden. The necropsy showed thickened aortic and mitral valves with atheroma of the aorta. There was no active disease, and the course of the case was aortic in character.

Again, a man aged 50, who had suffered from acute rheumatism at 8, 25, 36, and 49 years, had been failing for many weeks with progressive dyspnœa, dropsy, and the other signs of mitral asystole. There was aortic and mitral disease and death ensued. The necropsy showed mitral stenosis with shortening of the chordæ tendineæ, and calcification of both mitral and aortic valves, proof of a dead infection. The last illness had been afebrile.

Thirdly, death may occur in a recurrent attack of a more or less general rheumatic infection in which once more the valvular lesions are but an incident, but in which after death both recent and old injuries are demonstrable.

Thus, for example, a boy aged 10 years, who had suffered from acute rheumatism at 6, had been ill for twelve weeks before death. During this last illness there had been pericarditis, arthritis, and nodules, and there was also aortic and mitral disease. The necropsy showed recent pericarditis and

thickened aortic and mitral valves with, in addition, recent vegetations.

Fourthly, the disease of the valves may in a subsequent attack become the salient feature of the illness and show that persistence and virulence which is described as malignant. Thus, a boy aged 13 years, who had acute rheumatism with severe carditis at 10, was under observation for twenty-four weeks with pericarditis which subsided, and aortic and mitral disease which steadily progressed, accompanied by high fever and embolisms. The necropsy showed a recently adherent pericardium and malignant endocarditis of both aortic and mitral valves.

Fifthly, from the first valvular disease may be malignant in type, as in the case of a boy aged 7 years, whose sister and mother were the subjects of acute rheumatism, and who himself in an illness of four weeks developed first a polyarthritis, then a rheumatic erythema, and then pericarditis. The necropsy showed recent pericarditis, malignant mitral and simple aortic endocarditis.

Sixthly and lastly, every sort of transitional case may occur, of which we will give three examples :

Case 1. A boy aged 16 years, who had suffered from attacks of acute rheumatism at 6, 8, 10, and 12 years, was under observation in his final illness of eight weeks. During this period he developed a polyarthritis which subsided, and the combined valvular lesion with which he was already crippled steadily progressed with high fever and embolisms. During life, and after death, the case was described as a malignant endocarditis, but the vegetations upon the aortic and mitral valves were pointed out as small and resembling those of rheumatic endocarditis.

Case 2. A man aged 19 years had suffered from acute rheumatism at 11, 14, 17, and 18. Since the last attack his health had been failing for months, and a sore throat had preceded his final breakdown. Under observation his temperature never rose above 99.5° F., and when sudden death occurred the natural diagnosis was "heart disease." The post-mortem examinations showed a calcified mass on the aortic valve with malignant vegetations around it, and malignant endocarditis of the mitral valve.

Case 3. The third case is a clinical example only. A male

aged 38, who had previously suffered from three attacks of acute rheumatism, was under observation with the combined valvular lesion and cerebral embolism. For six weeks there was persistent fever with gradual asystole, but eventually there followed a slow and partial recovery, the temperature quieting down and the signs of hemiplegia improving. Such a case would be difficult to place with any confidence either as a simple or a malignant type of endocarditis.

This brief outline of salient examples brings us to the end of the introductory division of this paper, for we know that there will be no dispute as to the nature of the first three types we have exemplified, but that over the last three classes, namely the malignant cases supervening on old rheumatic endocarditis, the primarily malignant ones, and the transitional cases, there will be dissension of opinion, and it is these cases that bring to a focus the main issue of this contribution.

In the next section we shall frequently use the term malignant rheumatic endocarditis, but we do not use it, as has been asserted ought to be done, as connoting rheumatism complicated by streptococcal or other infections of the endocardium. It has been said that the name is only " permissible " in that sense ; we would, however, modify this statement, and we would claim that the name malignant rheumatic endocarditis is only permissible when it is used to express the fact that the diplococcal rheumatic infection may produce a malignant endocarditis.

Section II

I. *The Establishment of a Working Basis for the Thesis*

It appears to us that the most simple and direct method of presenting our facts is to give first of all examples of rheumatism with mitral and aortic disease which we hold to establish the following claims : (1) That acute rheumatism may cause aortic and mitral endocarditis. (2) That this endocarditis may eventually prove malignant, although coincident with the appearance of this malignancy other non-malignant or simple manifestations of acute rheumatism may appear and quiet down. (3) That the endocarditis in these malignant cases is caused by a strepto-diplococcus indistinguishable from that obtained from simple rheumatic endocarditis. (4) That

this strepto-diplococcus will produce in animals on intravenous injection both simple carditis and malignant endocarditis.

CASE 1. A boy, aged 10 years, was admitted suffering from active heart disease. Twelve months before he had had a severe attack of acute rheumatism, during which both the mitral and aortic valves were damaged. His final illness had commenced six weeks before, with breathlessness, anæmia, and wasting, and shortly after admission pericarditis developed. Two weeks later arthritis of the ankles and knees appeared. There seemed very good reason to look upon this condition as the result of another attack of severe rheumatism, a view favoured by the disappearance of the pericarditis and arthritis. In spite, however, of these signs of improvement the temperature remained high and the child lost ground. The explanation that now seemed feasible was that there was an unusually intractable simple endocarditis in progress, but during the next two months infarctions, sweating, anæmia, and fever pointed to the condition as malignant. Death occurred from sudden heart failure.

The necropsy demonstrated a generally adherent pericardium of recent date, the subsidence of all arthritis, extensive malignant endocarditis of the aortic and mitral valves, and renal and splenic infarctions.

A pure growth of strepto-diplococci was obtained from the valves, indistinguishable from that we have isolated from simple rheumatism. The first rabbit intravenously injected developed polyarthritis and malignant endocarditis of the *aortic and mitral valves*. The diplococcus was recovered in pure culture. The second developed malignant aortic endocarditis ; the third, polyarthritis and simple cardiac dilatation ; the fourth, malignant mitral endocarditis ; the fifth, general pericarditis and polyarthritis ; the sixth, polyarthritis only.

It appears to us that this case illustrates the four points we have put forward as rigid tests of our contention. We have the rheumatic origin of the lesion, the non-malignant evidences of active rheumatism during the final illness, and the complete experimental chain of evidence.

The next case (Case 2) is not quite so complete because of the absence of a multiple arthritis during the final illness.

CASE 2. A boy, aged 13 years, had suffered from severe rheumatic fever at the age of 10, leaving him with mitral and

aortic disease. For two months previous to his coming under observation he had been ill with precordial pain, dyspnœa, anæmia, and wasting. He was evidently suffering from active carditis, and succumbed after an illness of four months. Throughout the whole of this time there was irregular fever, and there was considerable enlargement of the spleen with other signs of a progressive endocarditis.

The necropsy showed general and recent pericardial adhesions, malignant aortic and mitral endocarditis, and a large spleen with infarctions.

A pure growth of strepto-diplococci was obtained. The first rabbit injected developed a mitral murmur for a while and eventually died many weeks afterwards—when no lesion was forthcoming. No. 2 died of malignant mitral endocarditis with infarctions. No. 3 died with simple mitral endocarditis and dilatation. No. 4 died of fibrinoplastic pericarditis. No. 5 died with general recent adhesion of the pericardium.

II. *Histological Support*

For many years emphasis has been laid upon the frequency of a history of a previous attack of rheumatic fever in cases of malignant endocarditis, and it is this that has led to the suggestion that antecedent damage to the valves favours the development of the malignant endocarditis.

With this view we are in agreement, but our explanation differs very distinctly from that usually accepted. First of all, however, we would point out that those who have opposed our views upon acute rheumatism have strangely neglected to publish and show any microscopical studies of the valvular lesions of rheumatism and malignant endocarditis in their various phases in man and animals. Yet this omission is, we think, a serious defect in their case, for in experimental endocarditis it is possible to trace every step from the earliest invasion of the valvular tissues to the exuberant malignant vegetation, and in human endocarditis to study nearly every phase of simple and malignant endocarditis and the methods of their healing.

If rheumatic endocarditis is not infective in origin it is remarkable that its lesions are indistinguishable from those of an infective process. If, on the other hand, it is the result of some unknown infection it is interesting to find that microscopy

is unable to distinguish between the nature of the results produced by this infection and the malignant endocarditis that may occur in the rheumatic.

It is also interesting to find that in the malignant form numerous strepto-diplococci can be demonstrated in the vegetations and are generally admitted to be the cause of the lesion, but that in simple endocarditis, in which the strepto-diplococci can also be demonstrated—though in scanty numbers, for simple endocarditis does not kill—the causal nature of these bacteria is brushed aside. This is the more remarkable when it is pointed out that the experimental lesions of simple and malignant endocarditis, when obviously caused in both instances by the diplococcus isolated from the human lesions, show the same variation in the number of diplococci in accord with their nature, a point we demonstrated to the Pathological Society of London in 1900.

Although there may be difficulty in isolating the diplococcus from rheumatic lesions, a fact which has been forced upon us, we may add rather to our surprise, through the reports of other pathologists, we can hardly think that there can be any justification for a failure to demonstrate diplococci in acute simple rheumatic endocardial lesions. This is but a matter of accurate technique and sufficient diligence, and that this may not seem a boast, we will support it by a quotation from a recent paper in *Heart* by Dr. H. G. Butterfield, Graham Research Scholar in University College Hospital Medical School. This writer, undertaking an entirely independent research upon acute carditis and heart-block, of which we were quite unaware, reports thus on the mitral valve of a case of classical rheumatic carditis :

"Bacteriological examination showed the presence of numerous Gram-positive diplococci with a tendency to short chain formation and in some cases to only partial retention of the methyl violet stain used. Some of these organisms were very small, and in general they were smaller than the ordinary streptococcus pyogenes." In our first paper on the Ætiology of Rheumatism we pointed out the minute size of the streptococcus and its only relative Gram-staining properties in tissues.

We may add that since seeing his sections we asked him to undertake the examination of another classical case in which Dr. Graham Forbes had isolated the micrococcus from the

pericardial exudation. In this he demonstrated the diplococci in the lesions of acute rheumatic pericarditis.

Why deny the causal agency of these micrococci in the simple lesions and accept it in the malignant, in the face of the positive experimental results that have been published and specimens of which may be seen by any interested person in the Hunterian Museum ?

There is, however, another point that is established by microscopy, which is that in the partially healed lesion of rheumatic endocarditis foci of necrotic tissue are found shut off by fibrous tissue or by proliferating tissue cells.

These foci we look upon as areas of danger in which the micrococci may long exist in a latent state. Further, it is, we believe, certain both from pathological study and clinical investigation that the vegetations often described in rheumatism as recent may have been of long standing. Even in a case of fatal carditis where there was much thickening and fibrous change in the mitral valve, we found on section that within the fibrous tissue there were still areas of necrotic tissue present. In such an occurrence there is nothing remarkable when it is remembered that sometimes rheumatic nodules may remain for many months, and that a section through the centre of one of these will show necrotic tissue ; and also that in chronic pericarditis the same phenomena can be demonstrated.

The examination of malignant vegetations throws very interesting light on the sequence of events. We need not delay by dwelling upon the well-known fact that in the most active part of the vegetations thousands of diplococci will be found. The point of importance is that in many of the slow cases there are well-marked attempts at cure in the vegetation, and if this process is studied we find that the necrotic areas become less filled with clearly staining micrococci and numerous refringent granules become visible. These are soon extremely difficult to differentiate from the groundwork in which they lie, and at last an area is reached where it is difficult to decide whether the necrotic tissue does or does not contain micrococci. The alteration in the staining properties of these micrococci in rheumatic endocarditis is deserving of close attention, and we are surprised that our critics have never commented upon this point, which has such a close bearing

upon the presence or absence of micrococci in this condition. Now if we turn for a moment to a study of some phenomena *in vitro* we find some suggestive points. The micrococcus of rheumatism does not thrive on agar-agar—a fact repeatedly ignored. If, however, we sow from this poor culture on to a mixture of bouillon, lactic acid, and milk, and the growth recovers sufficiently to clot the milk, we find that on examination of the amorphous clot numerous micrococci are beginning to appear. At first it is difficult to be sure whether one is looking at milk clot or micrococci, later the micrococci take the stain well, and later still they form obvious chains. This reverse process is very suggestive and leads us to believe that the necrotic tissue in damaged valves may contain micrococci much more frequently than is thought.

Our interpretation of the tendency for malignant endocarditis to occur in the damaged valves is, then, that circumstances of increased virulence arise and latent micrococci *in* the valves produce this change in the lesion. This inception of a new virulence is not peculiar to the rheumatic infection.

Even these results of microscopy do not exhaust the valuable assistance that can be obtained from this branch of inquiry, and we must confess to a slight feeling of injustice when our investigations have been criticised as being largely dependent upon cultures from the throat, which were open to the most serious error. Such cultures undoubtedly are, and our work in this direction was not attempted until we had isolated the micrococcus from all the important lesions and studied it by experiment in culture and in the human and animal tissues. The last points brought out by a study of the microscopy are these: that in some cases of very acute simple rheumatic endocarditis, such as occur, for example, in rare cases of fatal chorea, the vegetations, although minute, contain within them vast numbers of the micrococci. Such a section is indistinguishable from that through a malignant vegetation, and we have shown such examples on more than one occasion. Again, it is not rare to find in a fatal malignant endocarditis of the aortic and mitral valves *simple vegetations upon one and malignant upon the other.* On this account we have maintained that the essence of malignancy is not the size of the vegetations but the number and relative virulence of the micrococci, a statement borne out by the undoubted fact to be recognised

in our series, that a case which has been diagnosed as malignant may at the necropsy only show minute vegetations.

III. *Support from Blood Cultures*

We must now turn to the results of blood cultures which are taken during life in cases of acute rheumatism and malignant endocarditis. These have in our opinion been made responsible for statements which appear to us hardly justified by facts, for they require a very open-minded consideration of the pathological processes in acute rheumatism. To us the actual results that are obtained, far from militating against the view we hold upon the causation, lend distinct support. If we interpret the reasoning of our critics aright it is as follows: In many cases of malignant endocarditis a streptococcus is obtained by blood cultures, but in simple acute rheumatism the results are negative, therefore malignant endocarditis in the rheumatic is an epiphenomenon. We cannot accept these premisses or their interpretation. First let us ask the unbiased inquirer to picture the exact nature of the processes in acute rheumatism and we will postulate the original infection as tonsillar in origin. There is at once a gap in our knowledge which is not likely to be easily bridged over, and that is any idea of the number of micrococci which gain access to the blood stream. It is conceivable in the predisposed that a small infection only is requisite, and that this original supply multiplies in the local lesions. We do not yet know the number of micrococci that are sufficient in such people to produce a definite lesion; probably they are very few. This, however, is clear, that acute rheumatism consists of a number of *local foci* of infection in the tissues, and is not a general septicæmia. Further, there is great resistance to the disease, and the bacteria are rapidly destroyed in the blood and in these tissues. Now this being the case, it seems to us exceedingly unlikely that the withdrawal upon one or two occasions of some 5–10 c.c. of blood from the general circulation is going to yield a positive result. Why should it? If such an event were the rule we certainly should need to recast the pathology of this infection. Nevertheless in very severe and virulent cases with many grave lesions and evidences of systemic poisoning a positive result might be obtained. This is precisely our own experience, for all the cases of acute rheumatism in which we have succeeded

have been of that type. Thus, for example, a girl aged 17, the victim of chorea at 12, and rheumatic fever at 15 years of age, was seized with acute illness commencing with sore throat, multiple arthritis, and purpura. She was admitted under Dr. D. B. Lees for fever, multiple arthritis, severe purpura, and general carditis, pericardial friction appearing eight days after admission. Venesection was ordered on two occasions, and on both a pure culture of strepto-diplococci was obtained. Three months later the patient had so far improved as to be allowed on a couch, but asystole gradually developed and death ensued.

The post-mortem examination showed recent pericardial adhesions; the mitral aortic and tricuspid valves were all thickened, but there were no recent vegetations, still less evidences of malignant endocarditis, recent or old. The cause of death was myocardial disease from the severe carditis.

Here is proof that during the acute course of a severe rheumatic fever strepto-diplococci can be isolated from the circulation, and incidentally conclusive evidence that such a result was not due to agonal infection. This result is one of very real importance, for it disproves the loose statement that is sometimes heard, that the isolation of bacteria from the blood in active heart disease is proof of malignant endocarditis.

We must add, though it is perhaps obvious, that to look upon a positive culture of streptococci from the blood in a case of malignant endocarditis as evidence that the infection is not rheumatic is, in our opinion, quite unjustifiable. The rheumatic diplococcus in fluid media tends to become streptococcal in character, and believing, as we do, in a rheumatic malignant endocarditis we should expect a streptococcus might be obtained in such cases.

We would venture to add that the great majority of investigations in this country upon malignant endocarditis stop short of throwing any real light upon the essential point in dispute, for they almost always end either with the statement that a streptococcus was isolated, or with some primitive remarks upon the morphology, which we look upon as valueless, as we note also does Beattie, or with an attempt at classification by some laboratory tests *in vitro* which we and others cannot accept. What more, it may be fairly asked, would we demand? Our answer is, a careful series of experimental and histological investigations. If as a

result of these both malignant endocarditis and simple rheumatism result, the answer can be given as nearly as is possible in the present stage of our knowledge. Experimental proofs far outweigh in our opinion tests *in vitro*.

We have had other cases of acute rheumatism which have recovered and from which we have isolated the diplococcus from the blood stream, but this one, from the fact that there was a necropsy, stands out as a clear proof of the nature of the illness.

When we have a malignant endocarditis in rheumatism we have an unusual situation to deal with, in that there is then a focus teeming with micrococci actually impinging on the general circulation. Under such circumstances it is only to be expected that blood culture will prove to be positive in a far greater proportion of attempts, and if such were not the case we should have also to recast our views upon the pathology of this affection. Yet even in these circumstances, if the disease is of low virulence and the blood examination be made early, repeated negative results may be obtained by skilled bacteriologists—an event which is again only to be expected, but does not justify the assertion that the case is not malignant.

It is clear that we differ in one important respect from our critics upon this question of blood culture, for we dispute the statement that results in acute rheumatism are *always* negative.

IV. *Additional Evidence from a Study of the Series of a hundred Cases*

We believe now that we have reasonably established a claim to adopt this attitude toward cases of malignant endocarditis which are associated with previous acute rheumatism or which commence as attacks of rheumatism, viz. that the onus of proof that such are not rheumatic rests with those who deny that such a condition exists.

It must not be expected that in this series of a hundred examples of mitral and aortic cases from various sources complete chains of evidence are to be forthcoming, seeing that few physicians look upon the malignant types from our point of view, and that no bacteriologist, unless devoting himself to such a special study, will be likely to have made more than the routine investigation of the blood or vegetations. Then again, in the

non-malignant cases the lesions have often been considered as examples of heart disease and no particular stress laid upon them as phases in a prolonged rheumatic infection. Our evidence must then be of necessity fragmentary, but it is lawful for us, we think, to build up our thesis upon the carefully prepared basis of our complete investigations—that is, upon the four claims set out at the beginning of this section, strengthening the position by the aid of numerous other important fragments of evidence.

In order to avoid any suspicion that we are now trying to evade a plain issue, we will illustrate the character of our evidence by concrete examples of malignant endocarditis. The first case we quote is for the purpose of showing that we have weighed our evidence in every incomplete case.

A child, aged 4 years, had been ill ten days with arthritis of the shoulder, hips, and wrist joints; high fever and mitral disease. Pneumonic signs developed and death occurred.

In our opinion, if we published such a case as this as an example of a virulent first attack of rheumatism we should deserve the most drastic criticism.

The necropsy showed periostitis of the right femur, multiple suppurative arthritis, suppurative pericarditis, abscesses in the muscles, and early mitral disease. The *Staphylococcus pyogenes aureus* was isolated and was the cause of the illness.

On the other hand, a girl aged 11 had an attack of acute rheumatism at 9 and again at 10 years. Her final illness showed active carditis with persistent fever; no infarctions were observed. A strepto-diplococcus was isolated from the blood and at the necropsy malignant aortic disease was discovered with acute mitral of the simple type. Both valves showed former disease. The other viscera accorded with the diagnosis of a rheumatic infection. Such a case we claim to be rheumatic.

There is a very close clinical and pathological similarity in many of these cases of malignant endocarditis which becomes apparent from the short details of twenty-five examples that occurred in our series, and we feel justified in claiming some cases upon such clinical or clinical and pathological evidence, admitting at once that the proof is not complete, but believing the explanation as by far the most probable.

Case 1. A man aged 27 years had chorea as a boy, and an

attack of rheumatic fever at 26. He never laid up during the attack, but struggled on with his work, gradually losing ground. Compelled at last to take to bed, nine months after the neglected illness, he was found to have aortic and mitral disease with fever and died in under a fortnight. The necropsy showed malignant aortic and mitral disease and evidence of previous cardiac rheumatism.

This case we would explain as a rheumatic malignant endocarditis, probably produced by neglect of the acute rheumatism, an explanation which would necessarily fail if others can produce a series of examples of such cases for which a better solution can be given. We think that in this case also the endocarditis had probably been active the entire nine months and was only under observation in the terminal phase.

Case 2. The next case, which is of interest as an aortic and mitral one that cannot be included in our series, illustrates the difficulties that have to be encountered in any attempt at the study of disease in man.

A woman, aged 28, had suffered from rheumatic carditis after scarlet fever as a child and had never been well since her confinement thirteen months before. At the time of her confinement there was fever. After ten weeks of acute illness with purpura, paroxysmal fever, multiple embolisms, and progressive weakness she succumbed. No organism was isolated. The necropsy showed large vegetations, some with calcareous deposits in them, on the aortic valve and the anterior flap of the mitral. There were no abscesses, but white infarcts. Those who claim that this was a secondary infection of septic nature dating from the confinement have as strong evidence in their favour as those who would suggest that there was a lurking rheumatic endocarditis, which, in the puerperal state, awoke to virulence. The data are therefore insufficient and the case valueless on this account.

There is another difficulty to be faced over the determination of the nature of a carditis which is from the first malignant and is apparently the solitary lesion, or almost so. No one disputes the occurrence of a primary simple rheumatic endocarditis, that is, a pure cardiac rheumatism—and we naturally go a step further and ask, if this is admitted, why deny the possibility of the same, but in a malignant form, occurring in a first attack of rheumatism? Experiment proves that the

rheumatic organism can produce malignant endocarditis in a previously healthy valve.

EXAMPLE 1. Thus, for example, a child of fourteen years who gave no history of previous illness was seized with a sudden hemiplegia. There were irregular fever and wasting for seven weeks, and evidence of mitral disease. Blood culture was negative. Malignant mitral endocarditis and mitral disease were present with infarctions.

This was not a mitral and aortic case, but even if it had been we should not have included it in our series for lack of data. Nevertheless, it is most probable that this was an example of malignant rheumatic endocarditis.

EXAMPLE 2. The ground is far safer in the following example, already quoted in the first section, of a boy aged 7 years, whose mother and sister were the subjects of acute rheumatism, and who himself in an illness of four weeks developed polyarthritis, a rheumatic erythema, and then fatal pancarditis. Simple aortic and malignant mitral disease were found with pericarditis and the strepto-diplococcus isolated. In this case we have other manifestations of acute rheumatism. Such a case we look upon as undoubtedly rheumatic and as a link with that group which for the present purpose we may call transitional, in that they are clinically on the border line between simple and obviously malignant endocarditis.

EXAMPLE 3. Again, a girl of nine years had been ill four months with moderate and persistent fever. Polyarthritis had developed early in the illness and passed off; then severe mitral and aortic disease developed, with an enlarged spleen and multiple embolisms. After death, malignant aortic and mitral endocarditis was present.

We are aware, as one of the cases we have chosen has illustrated, that a polyarthritis in a child need not be rheumatic. A transient affection of the joints such as occurred in the above case is, however, much more suggestive of acute rheumatism than any other disease. When a series of cases of this kind is studied and all the evidence we have put forward deliberately weighed, we believe that we are justified in asking that those who dispute the nature of such an arthritis and endocarditis should produce definite facts in support of their contention, and not generalise from the well-known fact that there are many causes of arthritis.

We repeat that the preceding cases have been quoted in order to show that now that we are dealing with examples of malignant endocarditis which have not been completely investigated we have not assumed that they are necessarily rheumatic, but have balanced the evidence both for and against this view. The appended list from our series given in brief will enable the reader to form his own opinion upon the value of our evidence. We may add that from among the cases we searched through, nine examples of malignant endocarditis have been excluded because they were obviously the result of other infections, and fifteen were of uncertain nature and open to grave criticism.

It is very interesting to find in the list below all grades of virulence in the rheumatic process, and there are some cases which lead us to the next group. This is, we admit, quite an artificial one and called by us transitional because it bridges over the gap between the certainly malignant and the third group, which contains examples of acute rheumatism showing damage to the mitral and aortic valves of the simple type. As we pass to the transitional group the conclusive evidence becomes more and more difficult to obtain, because recovery is more likely to occur, and among these examples it may well have been that some were in reality of the malignant type and others of the simple. It is, if our view is correct, much more scientific to abandon these two terms simple and malignant and to substitute for them *active rheumatic endocarditis*. Such a term is much more satisfactory from every point of view, for it is less alarming to the patient ; it represents more accurately the true pathology and in no way blinds our eyes to the meaning of this activity when it reaches the degree in which the embolic phenomena and consequent systemic poisoning show that life is clearly threatened. Possibly the objection may be raised that such a condition of malignancy is utterly unlike any other manifestation in rheumatism, but we would point out that no other severe lesion in this disease could run a parallel course, however malignant it might be, for no other rheumatic lesion stands in the same relation to the general blood stream.

There is a statement that has been made about the relation of an attack of malignant endocarditis to previous rheumatic heart disease which we would traverse as a very misleading

one. It is to the effect that the two conditions, though associated, are as a rule quite independent of one another. Our series shows that there may be every variety of relation from immediate to remote, and we would add that because the relation is a remote one it is no proof at all that the malignant process is non-rheumatic. If any statement can be made about such cases it would be that the final condition, other things being equal, is more likely to be rheumatic than the result of any other infection.

Analysis of 100 *Cases of Rheumatic Aortic and Mitral Disease*

At this point before we give the first Table of cases illustrating rheumatic mitral and aortic lesions, it will be convenient to give a brief analysis of the complete series of 100.

1. *Sex.* 51 were females and 49 males.

2. The *age* incidence was as follows :

1–10 years . . .	15 per cent.
11–20 ,, . . .	32 ,, ,,
21–30 ,, . . .	23 ,, ,,
31–40 ,, . . .	15 ,, ,,
41–50 ,, . . .	10 ,, ,,
51–60 ,, . . .	3 ,, ,,
61–70 ,, . . .	1 ,, ,,
71–80 ,, . . .	1 ,, ,,

3. *Clinical groups.*

I. Cases developing from the first or in subsequent attacks malignant endocarditis, 25.

II. Cases on the border line between malignant and simple endocarditis, at least 13.

III. Cases illustrating acute rheumatic simple endocarditis, either as an incident in a widespread infection or as the predominant lesion, 33.

IV. Cases illustrating mechanical disabilities from the results of scarred valves :

A. Symptoms chiefly aortic : 6 cases.

B. Symptoms chiefly mitral : 22 cases.

4. *Fatal cases.*

44 cases were fatal—and some of the others who left the hospitals were taken away on account of their hopeless condition.

23 of the 25 examples of malignant endocarditis in Group I succumbed, and the remaining 2 only returned home in a dying condition.

4 of the 13 cases in Group II were fatal, but this group is an artificial one, made for the purpose of exposition, and is not to be looked upon as an entity.

11 of the 33 in Group III were fatal.

6 (2 in Group A and 4 in Group B) were fatal of the 29 cases in Group IV.

5. Bacteriological evidence is necessarily incomplete, for in the majority of cases none was made. 12 positive results were obtained in the 25 malignant cases and 6 were reported negative. The comparative success in this group is entirely in accord with the view of the pathology we have put forward.

Negative results in the simple rheumatic cases (Group III) are the rule, but there are exceptions. We would repeat that a single or even two such examinations of the blood are but little evidence of the presence or absence of an infective process when the result is negative, and that in our opinion far too much weight has been laid upon the occurrence of these negative results when the morbid processes in acute rheumatism are thoroughly realised.

6. The relation of the final illness, when fatal, to the last attack of rheumatism can be readily studied from our lists. The facts thus obtained are only relative, for, when a patient has been the victim of repeated attacks of acute rheumatism, the more closely the history is investigated the more frequently will be found evidence of some activity of the rheumatic processes between the definite attacks : these minor attacks are frequently not recorded and not mentioned by the patients.

7. All the observations upon the duration of the illness are also only approximate, but they serve to illustrate how prolonged the illness may be and how difficult it is to ascertain the commencement or the end of the active processes.

8. We would lay special stress upon the following histories from the groups of the malignant cases. First, three in which the malignant process dated from the first illness ; two in which it followed upon an attack of rheumatism six months before, from which illnesses the patients had never really recovered ; one in which there was a continuous history of failing health for twelve months after the fourth attack of

acute rheumatism; one in which the patient neglected a previous attack of rheumatism which had occurred less than a year before and after which he had been ill fed and had kept at work; one in which there had been failing health following a rheumatic polyarthritis five months previously.

These 8 cases out of a series of 25 show the close relationship of the rheumatic process to malignant endocarditis. 9 more illustrate the malignant endocarditis emerging from other and transitory symptoms of acute rheumatism. Thus 17 of these 25 cases show a close relationship to the occurrence of acute rheumatism.

Group No. I

Mitral and Aortic Cases Malignant in Type

Case 1. M., aged 10. Acute rheumatism at 9 years. Main symptoms of final illness: Admitted with mitral and aortic disease—developed transient polyarthritis and pericarditis. Later infarctions, persistent fever, &c. Approximate duration: 18 weeks. Bacteriology: Strepto-diplococcus isolated from valves. Result: *Death.* Malignant mitral and aortic, recent pericardial adhesion, white infarctions in spleen and kidneys.

Case 2. M., aged 13. Acute rheumatism at 10 years. Main symptoms of final illness: Mitral and aortic disease, transient pericarditis. Infarctions and persistent high fever. Approximate duration: 24 weeks. Bacteriology: Strepto-diplococcus isolated from valves. Result: *Death.* Malignant mitral and aortic, recent and old pericarditis, infarctions.

Case 3. M., aged 16. Acute rheumatism at 6, 8, 10, and 12 years. Main symptoms of final illness: Mitral and aortic disease, transient polyarthritis, fever, infarctions. Approximate duration: 8 weeks. Bacteriology: Strepto-diplococcus isolated. Result: *Death.* Malignant in the clinical course and in the post-mortem evidence of infarctions, but the vegetations on the two valves resembled those of *severe simple endocarditis.*

Case 4. F., aged 37. Acute rheumatism at 23 years. Main symptoms of final illness: Polyarthritis (subsiding), aortic and mitral disease, enlarged spleen, high fever, progressive course. Approximate duration: 18 weeks. Bacteriology: Strepto-diplococcus isolated from blood stream. Result:

Death. Simple aortic endocarditis. Malignant mitral. Infarctions in the spleen.

CASE 5. M., aged 7. Acute rheumatism: First attack. Main symptoms of final illness: Polyarthritis, pericarditis, erythema multiforme, acute aortic and mitral disease, high fever. Approximate duration: 4 weeks. Bacteriology: Strepto-diplococcus from pericardial fluid. Result: *Death.* Sero-fibrinous pericarditis, acute simple aortic, malignant mitral endocarditis.

CASE 6. F., aged 14. Acute rheumatism at 12 and 13 years. Main symptoms of final illness: Transient polyarthritis, mitral and aortic disease with continuous fever, evidences of infarction and nephritis. Approximate duration: 6 weeks. Bacteriology: Negative. Result: *Death.* The endocarditis was in character of the simple type; the lesions *qua* infarctions and nephritis, and the clinical course, were of the malignant type.

CASE 7. F., aged 21. Chorea at 7 years; acute rheumatism at 20 years. Main symptoms of final illness: Mitral and aortic disease with irregular fever, infarctions, and nephritis. Approximate duration: 16 weeks. Bacteriology: No report. Result: *Death.* Malignant type of vegetations on the mitral valve. On the aortic and tricuspid valves small vegetations.

CASE 8. F., aged 37. Acute rheumatism as a child and 6 months before final illness. Main symptoms of final illness: This illness imperceptibly followed upon an attack of rheumatic arthritis 6 months before. There were aortic and mitral disease. Moderate intermittent fever and infarction. Approximate duration: probably 6 months. Bacteriology: Negative. Result: *Death.* Malignant endocarditis of the mitral and aortic valves with infarctions in spleen.

CASE 9. M., aged 19. Acute rheumatism at 11, 14, 17, and 18 years. Main symptoms of final illness: This patient had never recovered from his last attack of acute rheumatism, but his symptoms increased after a sore throat, being those of mitral and aortic disease with slight fever never above 99.5° F. Sudden death occurred and the case was not suspected to be malignant. Approximate duration: over 12 months. Bacteriology: None made. Result: *Death.* Malignant mitral endocarditis recent and some vegetations on the aortic segments which were thickened and calcified.

CASE 10. M., aged 50. Acute rheumatism at 42 years. Main symptoms of final illness: An illness of some months' duration with transient polyarthritis in the articulations of the fingers. Aortic and mitral disease, later infarctions and purpura. The pyrexia persistent but at first mild, gradually increased in severity. Approximate duration: Some months. Bacteriology: Strepto-diplococcus from the circulation. Result: *Death.* Malignant endocarditis of the mitral, aortic, and tricuspid valves.

CASE 11. F., aged 16. Acute rheumatism at 12 years. Main symptoms of final illness: A long illness with polyarthritis, persistent fever, aortic and mitral disease, and infarctions. Approximate duration: 14 weeks. Bacteriology: Strepto-diplococcus from the circulation. Result: *Death.* No necropsy, but a case of the malignant type.

CASE 12. F., aged 11. Acute rheumatism at 9 and 10 years. Main symptoms of final illness: A comparatively rapid case in which there was high fever and severe aortic and mitral disease. Approximate duration: 7 weeks. Bacteriology: Strepto-diplococcus isolated from circulation. Result: *Death.* Small vegetations on the mitral, malignant on the aortic valve. No infarctions.

CASE 13. M., aged 27. Chorea as a boy; acute rheumatism at 26 years. Main symptoms of final illness: During the attack of acute rheumatism at 26 the patient would not rest but persisted with his work—steadily losing ground with cardiac symptoms until within 10 days of his death. During this time there was fever with severe mitral and aortic disease. Approximate duration: About 9 months; 10 days' acute illness. Bacteriology: No record. Result: *Death.* Malignant aortic and mitral endocarditis.

CASE 14. F., aged 16. Acute rheumatism at 12 years. Main symptoms of final illness: Admitted with multiple arthritis, which subsided, and also mitral and aortic disease. For some 3 months there was high fever. The spleen enlarged and was tender. Approximate duration: About 12 weeks. Bacteriology: No record. Result: *Death.* No post-mortem.

CASE 15. M., aged 11. Acute rheumatism at $7\frac{1}{2}$ years. Main symptoms of final illness: A case of progressive mitral and aortic disease—pericarditis with transient polyarthritis,

infarctions, enlarged spleen, and irregular fever. Approximate duration : 11 weeks. Bacteriology : Strepto-diplococcus from blood stream. Result : *Death*. Recent pericarditis. Malignant mitral and small aortic vegetations.

Case 16. M., aged 13. Acute rheumatism at 7 years. Main symptoms of final illness : A case of progressive mitral and aortic disease with irregular fever and infarctions. Approximate duration : 17 weeks. Bacteriology : Negative. Result : *Death*. Aortic malignant vegetations, mitral small vegetations.

Case 17. F., aged 9. Acute rheumatism : First attack. Main symptoms of final illness : Admitted with multiple arthritis and mitral and aortic disease ; there was moderate irregular fever throughout. The spleen enlarged, and emboli occurred, finally cerebral hæmorrhage. Approximate duration : 16 weeks. Bacteriology : No record. Result : *Death*. Malignant aortic and mitral endocarditis.

Case 18. F., aged 8. Acute rheumatism : First attack. Main symptoms of final illness ; Ill for 3 weeks with acute heart disease. Approximate duration : 3 weeks. Bacteriology : Strepto-diplococcus from aortic valve. Result : *Death*. Recent small vegetations on mitral and tricuspid, larger on aortic.

Case 19. F., aged 17. Chorea and morbus cordis at 12 years ; acute rheumatism at 15 years. Main symptoms of final illness : An acute illness with typhoidal character of fever; commencing with a stiff neck. Delirium, purpura, and infarctions followed mitral and aortic disease. Approximate duration : 4 weeks. Bacteriology : Strepto-diplococci from blood stream. Result : *Death*. Extensive mitral endocarditis spreading on the anterior flap of mitral and the neighbouring aortic cusp. Infarctions in spleen and kidneys.

Case 20. F., aged 24. Chorea at 8, 13, and 15 years. Main symptoms of final illness : Six months previously acute rheumatic arthritis, since then never well, severe aortic and mitral disease—persistent irregular fever, infarctions in spleen and kidneys. Approximate duration : 8 weeks. Bacteriology : Strepto-diplococcus from blood. Result : *Death*. No post-mortem.

Case 21. F., aged 48. Acute rheumatism at 38 years. Main symptoms of final illness : Failing health for 12 months—signs of cardiac asystole with irregular fever and aortic and

mitral disease. Approximate duration : Gradual. Bacteriology : No record. Result : *Death*. Malignant endocarditis, aortic and mitral.

Case 22. M., aged 28. Acute rheumatism at 18 years and minor attacks since. Main symptoms of final illness : Acute illness—typhoidal in character, high fever, aortic and mitral disease with multiple embolism. Approximate duration : 6 days' acute illness. Bacteriology : No record. Result : *Death*. Malignant aortic and mitral disease.

Case 23. F., aged 27. Acute rheumatism at 13 and 17 years. Main symptoms of final illness : Failing health for 8 months with moderate irregular fever. Aortic and mitral disease and renal and splenic infarctions. Approximate duration : 5 weeks' acute illness. Bacteriology : Negative. Result : *Death*. No post-mortem.

Case 24. F., aged 12. Acute rheumatism at 7 years. Main symptoms of final illness : Mitral disease, later developed aortic regurgitation with high irregular fever and hæmaturia. Approximate duration : 10 weeks. Bacteriology : Negative. Result : Left with the diagnosis of malignant endocarditis.

Case 25. F., aged 32. Acute rheumatism and chorea as a child. Main symptoms of final illness : 5 months' history of pains in the joints and limbs, 6 months under observation with irregular fever, aortic and mitral disease, pallor and emaciation. Approximate duration : 11 months. Bacteriology : Negative. Result : Left with active fever thought to be malignant.

Group II

Transitional Cases

When experimental endocarditis is produced with the diplococcus, whether isolated from a simple or malignant rheumatic endocarditis, every grade of severity may result. Recovery may occur or speedy death, and vegetations of all sizes may develop. It is impossible when dealing with this experimental endocarditis to justify the use of the terms " simple " and " malignant," and it is evident enough that the particular result is a question of the virulence of the cardiac infection. If this is the case with a small animal such as a rabbit whose cardiac valves are so minute and whose resistance is so comparatively weak, it is much more evident in man, in

whom the resistance to the rheumatic infection is so considerable and in whom the infection we can hardly believe occurs in such a gross fashion as by the method of intravenous inoculation. One link, however, in the chain is necessarily wanting in human pathology. We are not able, when we wish to observe the particular phase of an endocarditis, to look and see.

Transitional cases of rheumatic endocarditis, by which then we imply cases hovering on the border line of the divisions, simple or non-infective, and malignant or infective endocarditis, are of frequent occurrence.

In records we repeatedly meet with cases which are thought to be malignant and have quieted down, or have been considered simple and proved to be malignant. From time to time a post-mortem examination shows us evidence of an old malignant process in a valve by the presence of a large calcified vegetation. There is, however, no necessity for this particular evidence, for the malignancy does not depend upon the size and shape of vegetations but rather upon the virulence and number of the infective agent.

As an example in illustration may be quoted the following case : A girl of twelve had suffered from an attack of acute rheumatism three months before she came under observation. From this attack she never thoroughly recovered and a relapse of polyarthritis occurred, with a slowly progressive endocarditis of the mitral and aortic valves. When death occurred, five months later from cerebral embolism, a calcareous mass of vegetation was found upon the cusp of the aortic valve, and on the thickened mitral valve there were small recent vegetations.

This group of transitional cases is purely artificial and is not likely to content anyone, for it is built up partly upon clinical, partly upon experimental, and partly upon pathological evidence, and in some cases reliance has to be placed upon one source, in others upon another source of evidence.

We have, we repeat, only used the term here in order to show how advisable it is to abandon the terms " simple " and " malignant " as applied to rheumatic endocarditis, and by the formation of such a group to do what little we can to break down the barrier caused by the terms " infective " and " non-infective " endocarditis.

The examples that we give in this group can be supplemented by others in Group I and Group III.

Group No. II

Transitional Cases. Linked to Group I by Cases 3, 6, 12, *and* 18 *in that Group*

Case 1. F., aged 10. Acute rheumatism: First attack. Main symptoms of final illness: Admitted for multiple arthritis and heart disease. Ran a course with moderate irregular fever. The spleen enlarged and the mitral and aortic lesions proved fatal. Approximate duration: 11 weeks. Bacteriology: No record. Result: *Death*. The vegetations on the mitral and aortic valves were quite small, but the condition of the spleen and course of the case were in accordance with malignant endocarditis. There was no pericarditis.

Case 2. F., aged 12. Acute rheumatism: An attack 3 months before, never well since. Main symptoms of final illness: For many weeks slowly losing ground with multiple arthritis. Aortic and mitral disease. Fever for the last 3 weeks continuous, and finally cerebral embolism. Approximate duration: 20 weeks. Bacteriology: Negative. Result: *Death*. The mitral valve was thickened and there were some recent small vegetations. The aortic showed a calcareous mass on one of the segments—suggesting a healed malignant vegetation.

Case 3. M., aged 46. Chorea at 9 years. Main symptoms of final illness: A long illness commencing with polyarthritis. Mitral disease was followed by the appearance of aortic disease. There was continued fever, with enlargement and tenderness of the spleen, and blood and albumin in the urine. Approximate duration: 16 weeks. Bacteriology: Negative. Result: There was *recovery* from all the acute symptoms. It is difficult to explain the clinical course except as due to a transient malignancy.

Case 4. F., aged 44. Rheumatic fever at 25 and 34 years. Main symptoms of final illness: Admitted with aortic and mitral disease with continuous irregular fever; developed hæmoptysis and sudden pain in the left side. Approximate duration: 9 weeks. Bacteriology: Negative. Result: There was a *slow recovery*. All the acute symptoms subsided.

CASE 5. M., aged 13. Acute rheumatism: First attack. Main symptoms of final illness: Developed aortic and mitral disease with irregular fever. The clinical diagnosis was malignant endocarditis. Approximate duration: 10 weeks. Bacteriology: Negative. Result: *Relieved.* All acute symptoms disappeared.

CASE 6. M., aged 38. Acute rheumatism: 3 attacks. Main symptoms of final illness: Aortic and mitral disease with persistent fever for 7 weeks and cerebral embolism. Later signs of asystole. Approximate duration: 12 weeks. Bacteriology: Negative. Result: *Relieved.* Eventually all acute symptoms subsided and the patient made a partial recovery.

CASE 7. M., aged 28. Acute rheumatism at 24 years. Main symptoms of final illness: Admitted for active mitral disease; developed aortic regurgitation with persistent fever for 12 weeks. No emboli noted. Approximate duration: 16 weeks. Bacteriology: Negative. Result: *Relieved.* Thought to be malignant, but the acute symptoms quieted down.

CASE 8. M., aged 58. Acute rheumatism at 30 and 42 years. Main symptoms of final illness: A case of aortic and mitral disease with irregular fever for 3 months and blood and albumin in the urine. Approximate duration: 12 weeks. Bacteriology: No record. Result: *Relieved.*

CASE 9. F., aged 22. Acute rheumatism as a child; repeated attacks since. Main symptoms of final illness: Admitted with aortic and mitral disease, irregular fever, hæmaturia, and ophthalmoplegia. Recovered partially, but 5 months later readmitted with nephritis. Approximate duration: 4 weeks. Bacteriology: No record. Result: *Death.* The necropsy showed old pericarditis. Thickened mitral and aortic valves, a large spleen. Large white kidneys, with scars of previous infarctions.

CASE 10. F., aged 25. Acute rheumatism at 17 years. Main symptoms of final illness: Admitted with slight fever; ophthalmoplegia, renal infarctions. Approximate duration: 7 weeks. Bacteriology: Negative. Result: *Relieved.*

CASE 11. M., aged 15–17. Acute rheumatism at 12 and 13 years. Main symptoms of first illness (at 15): Arthritis and mitral and aortic disease, fever. Approximate duration: 4 weeks. Bacteriology: None made. Result: Simple acute

rheumatism. Main symptoms of second illness (at 16): Carditis and high irregular fever for 8 weeks. Approximate duration: 12 weeks. Bacteriology: No record. Result: Suspected to be malignant. Main symptoms of third illness (at 17): Carditis with 100 days' fever, pleurisy. Approximate duration: 17 weeks. Bacteriology: Negative. Result: Suspected to be malignant but *recovered.*

CASE 12 F., aged 14. Acute rheumatism at 11 years. Main symptoms of final illness: Admitted with polyarthritis, aortic and mitral disease. There were no evidences of embolism, but persistent fever for 9 weeks. Approximate duration: 9 weeks. Bacteriology: No record. Result: *Relieved.*

CASE 13. F., aged 10. Chorea and rheumatism at 8 and 9 years. Main symptoms of final illness: Admitted with polyarthritis, aortic and mitral disease, persistent fever for 9 weeks. Approximate duration: 9 weeks. Bacteriology: No record. Result: *Death.* Adherent pericardium. Aortic and mitral endocarditis of the acute rheumatic type, but the spleen enlarged.

GROUP III

Acute Rheumatic Heart Disease (Simple Type)

This group needs no explanation. The classical examples are found in the young, and the fatal first attacks are valuable illustrations of the fact that death results from a pancarditis, and not from the simple endocarditis. Here we would again repeat that in most of the opportunities for examining the vegetations of simple rheumatic endocarditis the actual process in the valves is in a stage of retrogression; it is only in rare exceptions that a condition can be obtained comparable to an early experimental endocarditis in which an animal can be killed as soon as the signs develop.

In several instances the cases with recurrent attacks of rheumatism illustrate the increasing obstinacy of the cardiac infection, with its repetition, and also show that the relation of a recurrent attack to previous ones precisely resembles that which exists between the malignant cases and a previous attack of acute rheumatism, for the time interval may be short or long.

Group No. III

Acute Rheumatic Endocarditis. Linked up to Group II by Cases 11, 12, *and* 13 *in that Group and* 3, 9, *and* 10 *in this*

Case 1. M., aged 4½. Acute rheumatism: First attack. Main symptoms of final illness: Polyarthritis, subsiding. Aortic and mitral disease, pericarditis and nodules, persistent fever. Approximate duration: 12 weeks. Bacteriology: No record. Result: *Death.* Subacute pericarditis, acute simple aortic and mitral endocarditis.

Case 2. M., aged 9. Acute rheumatism: First attack. Main symptoms of final illness: 5 weeks' fever with arthritis, nodules, and aortic and mitral disease. Approximate duration: five weeks. Bacteriology: No record. Result: *Death.* Acute simple aortic and mitral endocarditis.

Case 3. F., aged 9½. Acute rheumatism: First attack. Main symptoms of final illness: Arthritis, carditis and chorea; persistent irregular fever. Approximate duration: five weeks. Bacteriology: Strepto-diplococcus isolated. Result: *Death.* Acute simple endocarditis, though aortic vegetations larger; resembling those of a malignant case. Recent pericarditis.

Case 4. M., aged 9. Acute rheumatism at 8 years (six months ill). Main symptoms of final illness: Acute endocarditis and nodules; nine weeks' fever. Approximate duration: ten weeks. Bacteriology: No record. Result: *Death.* Adherent pericardium. Mitral and aortic endocarditis, recent vegetations, thickened valves.

Case 5. M., aged 10–11½. Acute rheumatism: First attack at 10 years; second attack at 11½ years. Main symptoms of first illness: Arthritis, persistent fever for many weeks, of the typhoidal type; aortic and mitral disease. Approximate duration: twenty weeks. Bacteriology: None made. Main symptoms of second illness: Asystole. Approximate duration: two weeks. Bacteriology: No record. Result: *Death.* Thickened aortic valves, with minute vegetations, aortic atheroma.

Case 6. F., aged 7. Acute rheumatism at 6 years. Main symptoms of final illness: Arthritis. Continuous irregular

fever, aortic and mitral disease. Approximate duration : twelve weeks. Bacteriology : No record. Result : *Death*. Slight recent aortic endocarditis. Old and recent mitral.

Case 7. F., aged 6½. Acute rheumatism at 4 and 5 years with pericarditis. Main symptoms of final illness : Asystole, with slight fever. Approximate duration : five weeks. Bacteriology : No record. Result : *Death*. Mitral aortic and tricuspid endocarditis of the acute rheumatic type. No evidence of pericarditis.

Case 8. F., aged 16. Acute rheumatism : First attack. Main symptoms of final illness : Commenced with polyarthritis, ten weeks' fever, gradually subsiding. Aortic and mitral disease. Approximate duration : thirteen weeks. Bacteriology : No record. Result : *Relieved*.

Case 9. F., aged 6–8. Acute rheumatism : First attack at 6 years ; second attack at 7 years ; third attack at 8 years. Main symptoms of first illness : Arthritis, chorea, nodules, persistent carditis, aortic and mitral disease, waves of fever extending over many weeks. Approximate duration : At least eighteen weeks. Bacteriology : No record. Result : *Relieved*. Main symptoms of second illness : Carditis, persistent fever. Approximate duration : Twelve weeks. Bacteriology : None made. Result : *Relieved*. Main symptoms of third illness : Ten days' fever, asystole. Approximate duration : Ten days. Bacteriology : Strepto-diplococcus isolated from mitral valve. Result : *Death*. Recent and old pericarditis, aortic valves inflamed from base to margin.

Case 10. M., aged 11–16½. Chorea at 3 years, acute rheumatism at 11, 12, 14, 16, and 16½ years. Main symptoms of first illness : Aortic and mitral disease, nodules, persistent fever. Approximate duration : Twenty weeks. Bacteriology : No record. Result : Simple mitral endocarditis. Main symptoms of second illness : Sent in for "a rest," persistent fever and tachycardia for three weeks. Approximate duration : three weeks. Bacteriology : No record. Result : *Relieved*. Main symptoms of third illness : Three weeks' palpitation and fever. Approximate duration : Five weeks. Bacteriology : No record. Result : *Relieved*. Main symptoms of fourth illness : Ten weeks' pericarditis and carditis. Approximate duration : Twelve weeks. Bacteriology : Blood culture negative. Result : *Relieved*. Fifth illness. Result :

Sudden death. No post-mortem; probably the simple type. Note persistent carditis with fever.

CASE 11. F., aged 17. Acute rheumatism at 10 years and two attacks since. Main symptoms of final illness: Admitted with mitral regurgitations and slight fever; developed aortic regurgitations and died suddenly. Approximate duration: Three weeks. Bacteriology: No record. Result: *Death.* No post-mortem.

CASE 12. M., aged 22. Acute rheumatism at 11 and 17 years. Main symptoms of final illness: Multiple arthritis. Aortic and mitral disease with irregular outbursts of fever, synchronous with which there was precordial pain. Approximate duration: Eight weeks. Bacteriology: No record. Result: *Relieved.*

CASE 13. M., aged 22. Acute rheumatism at 18 and 20 years. Main symptoms of final illness: Five months' history of recurrent anginal attacks, also multiple arthritis, aortic and mitral disease and recurrent attacks of fever. Approximate duration: Eight weeks. Bacteriology: No record. Result: *Relieved.*

CASE 14. M., aged 50. Acute rheumatism in childhood and at 25 years. Main symptoms of final illness: Aortic and mitral disease, with irregular fever for seven days. Approximate duration: Six weeks. Bacteriology: No record. Result: *Relieved.*

CASE 15. F., aged 10. Acute rheumatism at 7 and 8 years. Main symptoms of final illness: Polyarthritis, aortic and mitral, tachycardia, high irregular fever followed by a normal temperature and relapse. Approximate duration: Five weeks. Bacteriology: No record. Result: *Relieved.* Severe type of simple carditis.

CASE 16. M., aged 38. History of acute rheumatism at 6; 12, and 21 years. Main symptoms of final illness: Mitral and aortic disease with three attacks of fever, in one of which an attack of pericarditis. Approximate duration: Ten weeks. Bacteriology: No record. Result: *Relieved.*

CASE 17. F., aged 20. Acute rheumatism at 6 and 12 years; chorea at 15 years. Main symptoms of final illness: Double mitral and aortic regurgitation with slight transient fever. Approximate duration: Four weeks. Bacteriology: No record. Result: *Relieved.*

Case 18. M., aged 25. Acute rheumatism: Several mild attacks. Main symptoms of final illness: Polyarthritis, transient fever, mitral and aortic disease. Approximate duration: Seven weeks. Bacteriology: No record. Result: *Relieved.*

Case 19. M., aged 32. Acute rheumatism at 11, 16, and 26 years. Main symptoms of final illness: Mitral and aortic disease, left with a rising temperature. Approximate duration: Thirteen weeks. Bacteriology: No record. Result: Left at own request, nature of endocarditis doubtful.

Case 20. F., aged 18. Acute rheumatism: Six attacks. Main symptoms of final illness: Mitral and aortic disease, three weeks' irregular fever, pericarditis, several relapses of fever. Approximate duration: Thirteen weeks. Bacteriology: No record. Result: *Relieved.* Severe type.

Case 21. F., aged 24. Chorea at 9 years; acute rheumatism at 16 years. Main symptoms of final illness: Mitral and aortic disease with slight fever. Approximate duration: Five weeks. Bacteriology: No record. Result: *Relieved.*

Case 22. F., aged 20. Acute rheumatism: First attack. Main symptoms of final illness: Multiple arthritis, aortic and mitral regurgitations, always a slightly swinging temperature. Approximate duration: Eleven weeks. Bacteriology: Blood culture negative. Result: *Relieved.* Note persistent slight fever.

Case 23. M., aged 13. Acute rheumatism at 11½ years. Main symptoms of final illness: Aortic and mitral disease, arthritis, nodules, slight fever. Approximate duration: Seven weeks. Bacteriology: No record. Result: *Relieved.*

Case 24. M., aged 27. Acute rheumatism at 21 years. Main symptoms of final illness: Dyspnœa, mitral and aortic disease, slight irregular fever. Approximate duration: Five weeks. Bacteriology: No record. Result: *Relieved.*

Case 25. M., aged 21. Acute rheumatism at 10 and 11 years. Main symptoms of final illness: Subacute arthritis, mitral and aortic disease, slight fever. Approximate duration: Three weeks. Bacteriology: No record. Result: *Relieved.*

Case 26. M., aged 24. Acute rheumatism at 11 years. Main symptoms of final illness: Arthritis, mitral and aortic disease, and irregular fever. Approximate duration: Seven weeks. Bacteriology: No record. Result: *Relieved.*

Case 27. M., aged 22. Acute rheumatism : First attack. Main symptoms of final illness : Arthritis followed by mitral and then aortic regurgitations, always a slight fever, never rising above 100° F. Approximate duration : Seventeen weeks. Bacteriology : No record. Result : *Relieved.* Note the mild but progressive course.

Case 28. F., aged 35. Acute rheumatism at 14 years. Main symptoms of final illness : Arthritis, mitral and aortic disease and slight fever. Approximate duration : Five weeks. Bacteriology : No record. Result : *Relieved.*

Case 29. F., aged 11. Acute rheumatism at 8 and 9 years. Main symptoms of final illness : Mitral and aortic disease ; only in hospital ten days. Approximate duration : Ten days. Bacteriology : No record. Result : *Relieved.*

Case 30. F., aged 34. Acute rheumatism : Six attacks. Main symptoms of final illness : Mitral and aortic disease. Approximate duration : Five weeks. Bacteriology : No record. Result : *Relieved.*

Case 31. M., aged 10. Acute rheumatism at 6 years. Main symptoms of final illness : Pericarditis, aortic and mitral disease, nodules and arthritis, fever for fourteen days, ill twelve weeks. Approximate duration : Twelve weeks. Bacteriology : No record. Result : *Death.* Thickened aortic and mitral with recent vegetations (small). Recent pericarditis.

Case 32. F., aged 19. Rheumatism and chorea at 13 years. Main symptoms of final illness : Severe aortic and mitral disease with continuous fever for five weeks ; anginal attacks. Approximate duration : Five weeks. Bacteriology : No record. Result : *Relieved.* Note prolonged fever, carditis, and angina.

Case 33. F., aged 38. Acute rheumatism at 14 years. Main symptoms of final illness : Mitral and aortic disease, admitted with transient polyarthritis and fever. Approximate duration : Five weeks. Bacteriology : No record. Result : *Relieved.*

Cases in Group IV

The last group of cases will not need any prolonged explanation, for they are examples of heart scars with consequent mechanical disabilities. There is a sufficient number of fatal

cases among them in which a necropsy has proved the reality of such an interpretation, and their chief importance is to emphasise the power that the human frame possesses to resist the rheumatic infection. This very fact bringing it strictly into line with other great infections only serves to throw into relief the overwhelming probability that these healing processes may also fail, as they do undoubtedly succeed, in such a struggle. What an assumption it must be to assert that such an infection as the rheumatic could always be overcome in the cardiac valves! Even if we were deprived of all the clinical, pathological, and experimental evidence we now possess such an assumption would be open to the gravest questioning, but with such evidence at hand it must surely be abandoned as a survival of an older pathology which existed when acute rheumatism was looked upon as of nervous or lactic acid origin. Old beliefs die very hard, and oftentimes in medical literature may be seen the strange results of attempting to graft upon an old stem the new shoots of another plant of knowledge. The relationship of rheumatism to malignant endocarditis is a beautiful example of such an attempt. Every sort of ingenious device has been invented to graft the old stem with the new shoots, but they have all failed.

Among the most remarkable must be placed that one which suggests that rheumatism is a mysterious and unknown disease akin to simple scarlet fever, upon which all the manifestations are to be grafted as secondary infections. When we can imagine on the one hand a scarlet fever which is not infectious and is without a rash save in exceptional cases, and on the other a rheumatism which is infectious and which possesses no manifestations except possibly a sore throat and an occasional rash, we may be able to appreciate the likeness between these two diseases. For us an infectious disease such as scarlet fever, whether complicated by secondary infections or not, possesses a peculiarity of its own, viz. its infectivity. Whereas acute rheumatism, deprived of its manifestations, is a disease still to be discovered, as also would be in our opinion a tuberculosis or pneumococcal infection without its manifestations.

Group No. IV

Chronic Heart Disease due to previous Rheumatic Endocarditis

A. Cases showing chiefly aortic symptoms

Case 1. M., aged 63. Acute rheumatism : Three attacks ; heart disease at 13 years. Main symptoms of final illness : Two days' illness. Sudden death, aortic type, mitral and aortic disease. Approximate duration : Two days. Result : *Death.* Calcified valves.

Case 2. M., aged 42. Much rheumatism. Main symptoms of final illness : Angina pectoris—dyspnœa, aortic and mitral disease. Approximate duration : Many weeks. Result : *Death.* Thickened valves and aortic atheroma.

Case 3. M., aged 40. Acute rheumatism at 27. Main symptoms of final illness : Mitral and aortic disease, angina pectoris. Approximate duration : Four weeks. Result : *Relieved.*

Case 4. M., aged 40. Acute rheumatism : Repeated attacks. Main symptoms of final illness : Mitral and aortic disease with angina. Approximate duration : Six weeks. Result : *Relieved.*

Case 5. F., aged 14. Acute rheumatism : Slight. Main symptoms of final illness : Mitral and aortic disease, pallor, pain in chest. Approximate duration : Nine days. Result : *Relieved.*

Case 6. M., aged 28. Acute rheumatism at 18 years and since. Main symptoms of final illness : Mitral and aortic disease, dyspnœa. Approximate duration : Seven days. Result : Left at his own request.

Case 7. M., aged 48. Acute rheumatism at 35 and 39 years. Main symptoms of final illness : Mitral and aortic disease, angina. Approximate duration : Three weeks. Result : *Relieved.*

B. Cases showing chiefly mitral symptoms

Case 1. M., aged 38. Acute rheumatism : Several attacks. Main symptoms of final illness : Alcoholism. Mitral and aortic disease, jaundice, dropsy, dyspnœa. Approximate duration : Eleven weeks. Result : *Death.* Sclerosis of aortic and mitral valves.

CASE 2. M., aged 50. Acute rheumatism at 8, 25, 36, and 49 years. Main symptoms of final illness : Mitral and aortic. Œdema, dyspnœa, &c. ; asystole. Approximate duration ; Many weeks. Result : *Death.* Calcified aortic and mitral valves ; shortening of chordæ tendineæ.

CASE 3. M., aged 72. Acute rheumatism at 17 years. Main symptoms of final illness : Mitral and aortic. Myocardial weakness. Asystole. Approximate duration : Four weeks. Result : *Death.* Thickened mitral and aortic valves. Atheroma.

CASE 4. F., aged 52. Acute rheumatism at 40 years. Main symptoms of final illness : Mitral and aortic. Asystole, with œdema, &c. Approximate duration : Four weeks. Result : *Relieved.*

CASE 5. F., aged 60. Acute rheumatism : Slight attacks. Main symptoms of final illness : Mitral and aortic. Asystole, with cyanosis and dropsy. Approximate duration : Five weeks. Result : *Relieved.*

CASE 6. F., aged 79. Acute rheumatism : Six attacks. Main symptoms of final illness : Mitral and aortic. Asystole—mitral type. Approximate duration : Five weeks. Result : *Relieved.*

CASE 7. M., aged 35. Acute rheumatism at 20 years. Main symptoms of final illness : Mitral and aortic. Alcoholism, asystole. Approximate duration : Five weeks. Result : *Relieved.*

CASE 8. M., aged 20. Acute rheumatism at 11 years. Main symptoms of final illness : Mitral and aortic. Asystole—mitral type. Approximate duration : Three weeks. Result : *Relieved.*

CASE 9. F., aged 18. Acute rheumatism at 13, 14 and 15 years. Main symptoms of final illness : Mitral and aortic. Approximate duration : Two weeks. Result : *Relieved.*

CASE 10. F., aged 26. Acute rheumatism : Repeated attacks. Main symptoms of final illness : Mitral and aortic. Severe asystole, mitral type. Approximate duration : Twenty-four weeks. Result : *Relieved.*

CASE 11. F., aged 20. Acute rheumatism : Six attacks. Main symptoms of final illness : Mitral and aortic disease. Signs of mitral asystole. Approximate duration : Four weeks. Result : *Relieved.*

CASE 12. M., aged 40. Acute rheumatism at 19 years. Main symptoms of final illness: Mitral and aortic disease. Signs of mitral asystole. Approximate duration: Ten weeks. Result: *Relieved.*

CASE 13. M., aged 48. Acute rheumatism at 12 and 38 years. Main symptoms of final illness: Mitral and aortic disease. Signs of asystole. Approximate duration: Some weeks. Result: *Relieved.*

CASE 14. M., aged 22. Acute rheumatism at 19 years. Main symptoms of final illness: Mitral and aortic disease. Signs of asystole, mitral. Approximate duration: Three weeks. Result: *Relieved.*

CASE 15. M., aged 22. Acute rheumatism at 16 years. Main symptoms of final illness: Mitral and aortic disease, prolonged asystole. Approximate duration: Eighteen months. Result: *Relieved.*

CASE 16. F., aged 32. Acute rheumatism at 14, 19, 21, 23, and 25 years. Main symptoms of final illness: Mitral and aortic disease, with palpitation. Approximate duration: Seven days. Result: *Relieved.*

CASE 17. F., aged 32. Acute rheumatism at 17 and 31 years. Main symptoms of final illness: Mitral and aortic disease, with signs of mitral asystole. Approximate duration: Four weeks. Result: *Relieved.*

CASE 18. F., aged 33. Acute rheumatism as a child. Main symptoms of final illness: Mitral and aortic disease. Palpitation, &c. Approximate duration: Ten days. Result: *Relieved.*

CASE 19. F., aged 21. Acute rheumatism at 11 and 12 years. Main symptoms of final illness: Mitral and aortic disease. Anæmia, palpitation, &c. Approximate duration: Many months. Result: *Relieved.*

CASE 20. F., aged 28. Acute rheumatism as a child and at 18 years. Main symptoms of final illness: Mitral and aortic disease. Asystole. Approximate duration: Many weeks. Result: *Relieved.*

CASE 21. M., aged 14. Acute rheumatism at 12 years. Main symptoms of final illness: Mitral and aortic disease. Severe asystole. Approximate duration: Four weeks. Result: *Death. Aortic and mitral valves thickened, adherent pericardium.*

CASE 22. M., aged 30. Acute rheumatism at 16 years.

Main symptoms of final illness : Mitral and aortic disease. Signs of asystole. Approximate duration : Three weeks : Result : *Relieved.*

We wish now to put very briefly our conception of acute rheumatism—or, as we would prefer to call it, rheumatism—side by side with the pictures of other similar infections.

1. First of all the gonorrhœal infection.

From a local focus in the urethra there may follow a systemic invasion producing multiple arthritis and other lesions, including a carditis. The arthritis may be transient, but often is exceedingly stubborn and drifts into a condition of rheumatoid arthritis. The heart affection may be a pancarditis, or a transient endocarditis, or a malignant endocarditis.

2. With the pneumococcal infection the lungs and pleuræ take the position that the heart occupies in rheumatism, but arthritis of all grades of severity may result, and also a carditis, in which suppurative pericarditis and malignant endocarditis are liable to develop.

3. In staphylococcal infections, from a local infection such as an acute osteo-myelitis, there may follow multiple arthritis and multiple nodular subcutaneous abscesses, myocardial abscesses, and acute malignant endocarditis may all result.

4. Virulent streptococcal infections of the type caused by the *streptococcus pyogenes* show a similar picture. The arthritis, if not exceedingly acute, is suppurative ; profound myocardial poisoning is much more frequent than endocarditis, and this, when it occurs, is usually malignant in type. A general septicæmia is frequent, and in classical cases the entire process differs widely from that of acute rheumatism. It is a difference in the type and not in the degree of virulence.

5. The rheumatic infection from such a focus as the tonsil may produce an arthritis and other lesions, including a carditis. Two features are well recognised. One is that the arthritis is usually transient, although we maintain that a rheumatoid arthritis may result from this infection. The other is the great prominence of cardiac lesions. Carditis is very frequent, and both simple and malignant endocarditis may result.

We believe that this conception of acute rheumatism as a peculiar streptococcal infection fills a gap in our knowledge of this important disease, in a way that is unequalled, not only

for its simplicity, but for the completeness of the explanation which it affords of the symptoms and course of the affection.

The strong hereditary element in the disease supports the view that the exciting cause possesses some peculiarity by which in these particular tissues it can form the special poisons that make it so definite an affection.

Concluding Remarks

We believe that the view we support in this research is not one of academic interest or a mere battle of words. It will be a distinct gain if we succeed in overthrowing the remarkable view that the nature of rheumatic endocarditis—whatever the infection may be—is always benign and requires an added infection to produce a progressive lesion. The survival of such a view implies such a subversion of the natural principles of the infective processes as to unsteady one's whole outlook upon these diseases. The disappearance of such a mystery, on the other hand, must be a clear gain to connected thought upon all rheumatic processes and a forward step in cardiac pathology.

Far more important is its bearing upon the clinical side of malignant endocarditis. The rheumatic form is no exception to the rule that it is a disease which is almost invariably fatal when the signs are well established. Theoretical considerations lead to the belief that occasional recoveries may occur, and there is good clinical evidence in support ; but these exceptions are rare, and our series alone shows the great fatality.

We are doubtful of the efficacy of serum or vaccine at present in use, though we would neither dispute the records of such recoveries while such treatment was being employed, nor the advisability of trying any method that holds out the least prospect of success.

It is the prophylaxis that is encouraged by our investigations. There must clearly be some peculiar factors at work to produce the progressive endocarditis, and we sometimes find suggestive evidence in support of this. The cardiac rheumatism may have been neglected, the patient ill-fed, the surroundings unhealthy. Anæmia—a prominent feature of some rheumatic attacks—may have persisted, and this in our opinion favours the malignant process. The danger of large unhealthy tonsils in the rheumatic is well established, and this danger can be

cautiously dealt with. Above all, we believe that more clinical study is necessary of the course and history of acute rheumatic endocarditis. We believe that a smouldering activity of the rheumatic process is more common than is suspected, and very possibly we may not yet possess the necessary clinical accuracy for ascertaining the limits of this activity. This seems the more likely when we bear in mind that even a gross and progressive lesion may elude our observation until the end is close at hand.

There is more hope that we may protect a patient against the development of a known danger than against a mysterious secondary infection which prefers scarred valve tissues and which appears usually without any particular cause or reason.

The disappearance of the terms "malignant," "infective," or "pernicious" as applied to endocarditis will be a great advantage, and the substitution of the term "active" will answer every purpose, for the physician can judge of the degree of this activity by the well-known signs that may arise. "Active tuberculosis" expresses sufficiently a progressive pulmonary lesion, and we need no term "malignant tuberculosis" to bring home to us the fact that the activity is getting beyond all control. Why then use such a term as "malignant endocarditis," or perpetuate such an unproven conception as a non-infective endocarditis, by the use of the adjective "infective"?

REFERENCE

Guy's Hospital Reports, 1911, p. 193.

PART II

SUB-GROUP F

THE CONCLUDING PAPERS OF THE SECOND PART OF THIS VOLUME DEAL WITH THE VERY INTERESTING PROBLEMS OF THE METHODS OF ORIGIN OF APPENDICITIS, AND THE RELATION OF APPENDICITIS TO RHEUMATISM. THE FIRST PAPER WHICH WAS WRITTEN ALMOST EXACTLY TEN YEARS BEFORE THE SECOND, HAS BEEN PLACED WITH THE OTHERS IN ORDER TO MAKE THE INVESTIGATION MORE COMPLETE. THE LAST PAPER HAS NOT BEEN PUBLISHED BEFORE, AND IS INCLUDED AS A FURTHER EXPRESSION OF OUR VIEWS UPON THE EXPERIMENTAL, CLINICAL, AND PATHOLOGICAL ASPECTS OF THE SUBJECT.

PAPER NO. XXIV

ARTHRITIS IN ASSOCIATION WITH PERITYPHLITIS

(Reprinted from *Transactions of the Medical Society of London*, vol. xxiv.)

In this paper, written in 1900, *the subject of appendicitis and rheumatism is discussed from various points of view. The opinions of those who believe that there is a direct connection between the two diseases are given, and some clinical evidence added in support. On the other hand, the possibility of other explanations of the apparent association are put forward, and examples are given of pyæmic conditions following appendicitis and simulating rheumatism. If there was a direct connection between rheumatism and appendicitis it appeared to us that the rheumatic infection of the appendix was a lesion which did not occur in acute rheumatism of the ordinary type. It was, however, conceivable that rheumatism affecting the alimentary canal might spare the other systems, just as some cases of rheumatic arthritis appear to locate themselves in the joints alone or in the joints and muscles, sparing the heart and nervous system.*

The association of arthritis with perityphlitis, though not a common occurrence, has attracted some attention, because it has seemed likely to throw light upon the ætiology of perityphlitis. Some observers, who have noticed this association, have advanced the suggestion that rheumatic fever is an important cause in the production of perityphlitis and have brought forward evidence in its support. This evidence for convenience is classified under four headings. Firstly, there is the occurrence of perityphlitis in the subjects of acute rheumatism; secondly, the occurrence of a polyarthritis, resembling that of acute rheumatism, coincident with, or shortly after, an attack of perityphlitis; thirdly, there is the reaction of some cases of perityphlitis to treatment with salicylates; and lastly, there is the structural analogy of the tonsils and appendix vermiformis.

To take the last of these first, Bland-Sutton, Kelynack, Mayo Robson, and others have proved that lymphoid tissue is present in the appendix. Those who support the rheumatic hypothesis point out that cold is a factor in appendicitis and also in rheumatism. They compare the tonsil and the appendix, and, guided by the undoubted fact that tonsillitis is frequently the earliest symptom of rheumatic fever, conclude that, in some cases, perityphlitis may also be an early symptom of the same disease. This argument is both interesting and ingenious, but doubtless requires further support from clinical and pathological observation.

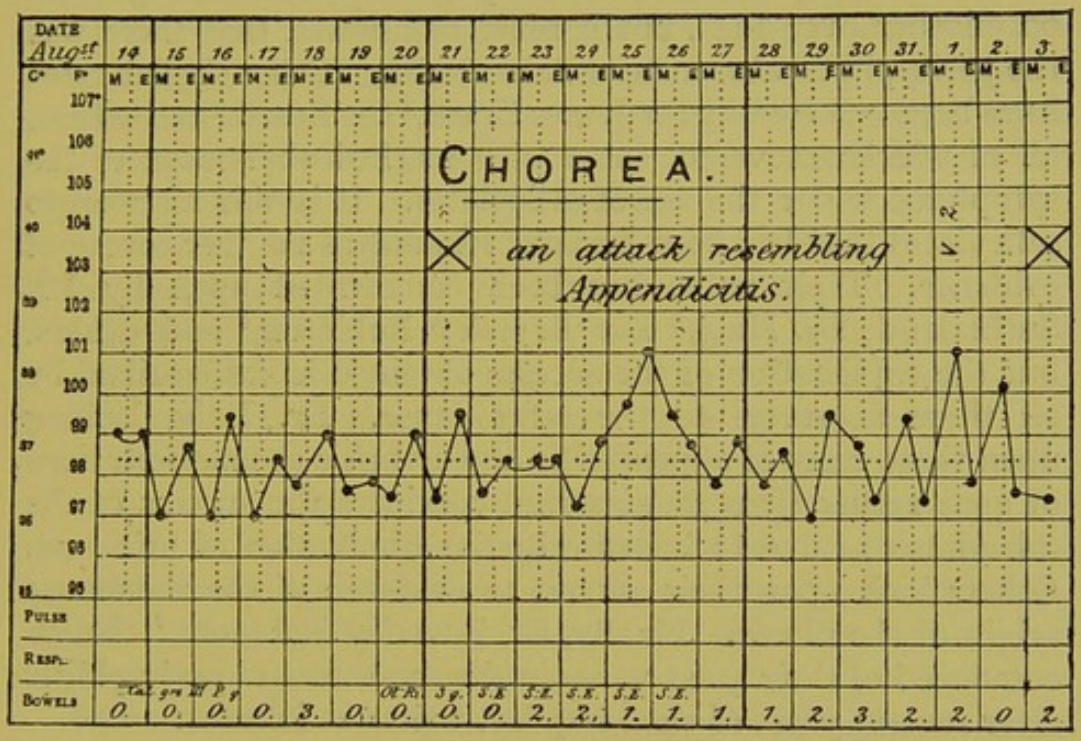
The occurrence of perityphlitis in the subjects of acute rheumatism has been called attention to by Dr. G. A. Sutherland in a paper published in the *Edinburgh Hospital Reports* of 1895.[1] Dr. Sutherland published in this paper examples of this association, occurring in children, in whom there was a personal and also a strong family history of rheumatic fever. The attacks of perityphlitis, judging from the reports, were mild, as for none of them was an operation required. This from the strictly scientific aspect detracts necessarily from their value, for it is the absolute proof, either by operation or necropsy, that is especially desirable in a question of such a nature as this one.

We have quite recently met with a case resembling in some respects those described by Dr. Sutherland, and for leave to use the notes of this case are indebted to Dr. W. S. Colman. A boy, aged 11, was admitted in August to the Hospital for Sick Children, Great Ormond Street, for rheumatic chorea. The chorea was not severe but stubborn ; the heart was dilated, and there was a faint systolic murmur. While in the hospital the bowels became obstinately constipated, and pain was complained of in the right iliac fossa. The bowels, in spite of treatment, were only thoroughly opened upon one day between August 14 and 22. Synchronous with the pain, there was a rise of temperature. The fever was intermittent, lasted for about fourteen days, and reached at its maximum 101°. The tenderness over the right iliac fossa continued, a definite mass could be felt, and vomiting occurred upon two occasions. The bowels were kept open by enemata, and gradually the fever and internal symptoms disappeared.

This case is plainly inconclusive, for all the symptoms might

have been the results of constipation, and even if there was, as seemed probable, some actual appendicitis, the occurrence of chorea may have been a mere coincidence.

There is, we believe, a general agreement among those who have especially studied rheumatism in childhood, that such children frequently suffer from obscure abdominal pains. Such experience as we have had has given us the impression that these pains are generally paroxysmal, and usually referred above the umbilicus to the epigastric region. They have



interested us, because it has seemed difficult to explain them satisfactorily, though it is probable that in some cases the pain is situated in the abdominal muscles.

The occurrence, in association with perityphlitis, of multiple joint affections, having the character of a rheumatic arthritis, has been recorded by several observers, and a very complete case was published by Dr. Burney Yeo in the *British Medical Journal* for June 16, 1894.[2] A girl, the subject of an acute attack of rheumatism some months before, had been ill for a fortnight with pains in the elbows and knees and general malaise. She then developed severe abdominal pain, and was admitted upon April 16 to King's College Hospital with a definite and severe attack of perityphlitis. There was temporary improvement,

but four days afterwards, with a recrudescence of the perityphlitis, her elbows and wrists swelled and became extremely tender, and an apical systolic murmur present on admission became louder and more definite. The perityphlitis was sufficiently severe to raise the question of pyæmic metastases, but complete recovery followed without operation. The temperature and joint lesions reacted to a marked degree to treatment by salicylates. There was this unusual feature about the case that the temperature was remarkably high and irregular for rheumatism, reaching on one occasion 105°, and on another over 104°, but it must be allowed that there was the perityphlitis also to be reckoned with. Other similar cases have been reported by Sir James Grant,[3] Dr. Brazil,[4] and others, all of which recovered, some with marked abatement of the symptoms under the use of salicylates. It is this reaction to salicylates that has been brought forward as another source of evidence. Their value has been commented upon by Dr. Sutherland, Dr. Haig,[5] Dr. Beverley Robinson,[6] and others, but the explanation of the success obtained is not ascribed by all these observers to the same cause. Dr. Haig, looking upon these cases of appendicitis and arthritis as manifestations of gout rather than rheumatism, considers the success of the salicylates as due to increase in the elimination of uric acid. Others look upon their success as evidence of the rheumatic origin of the illness. Finally, Dr. Beverley Robinson,[7] though convinced of their great value in the treatment of perityphlitis after several years of close inquiry, writes as follows :

"I do not remember personally to have seen an attack of acute articular rheumatism either distinctly precede or follow evident signs of appendicitis, and to be connected with it in such a way that the relation of the two affections was clearly defined."

The inference, we think, is that in such cases as these, though salicylates may be of value for the relief of symptoms, their success is no proof of the rheumatic character of those symptoms. This is a view maintained by several authoritative writers, and in this paper we are able to bring forward some evidence in its support.

To recapitulate at this point, it may be justly said that though there is some evidence in support of the rheumatic

origin of perityphlitis, it is hardly as yet sufficient for a scientific proof, and the possibility of coincidence in two diseases of common occurrence has always to be taken into account. During the two years that one of us was medical registrar and pathologist at St. Mary's Hospital, he was enabled to follow up this question, especially upon the clinical side, and investigated sixty cases of perityphlitis, with reference to this question of rheumatism. As his guide he took the manifestations of the rheumatic state as laid down by Dr. Cheadle in the Harveian Lectures for 1888, and the observations were made upon cases of every grade of severity. In thirty-one the diagnosis was confirmed by operation, and only undoubted examples were chosen ; forty were first attacks, the remainder were recurrent, and eighteen of these patients were subject to repeated relapses, so that all the types of this disease were represented. The ages varied from 6 to 57 years. In none of these cases—and this is in agreement with Dr. Beverley Robinson—could he trace any connection between the attack of perityphlitis and an attack of rheumatism, though in a certain number there was a history, more or less doubtful, of a previous rheumatic attack. Thus, in eleven cases there was a family or personal history, and in five a personal history. In one case there was a definite systolic murmur, but this patient, in addition to perityphlitis and a previous arthritis, had suffered from typhoid and dysentery, and was apparently susceptible to most infections.

There were in the series two cases of multiple arthritis occurring shortly after the onset of perityphlitis.

Two papers, one by Piard [8] upon "Metastatic Suppurations in Connection with Appendicitis," and one by Akerman [9] upon "Experimental Osteo-myelitis," seem to throw light upon these difficult cases.

Dr. Piard, in the Paris *Archives de Médecine* in 1896, though he made no observations upon arthritis, gave numerous examples of visceral, pleural, and intra-muscular abscesses occurring after appendicitis, and emphasised the important clinical fact that such metastases are especially liable to occur in those cases in which the local evidences of perityphlitis are absent or but slightly marked. Akerman, in the third volume of the "Archives of Experimental Medicine," published some interesting results obtained by intravenous inoculations of

the bacillus coli into young rabbits. If pure cultures were injected of sufficient strength to allow characteristic lesions to occur, a multiple osteo-myelitis developed, and, with this, changes in the neighbouring joints. Usually the fluid within them was increased and varied in character with the virulence of infection. It was sometimes clear, sometimes turbid, and sometimes purulent. In several instances the bacillus coli was demonstrated in these joints. The condition developed more slowly than in ordinary suppuration.

Again, numerous investigators [10 11 12] have demonstrated the importance of the colon bacillus in perityphlitis, and this organism has been demonstrated in the metastatic visceral abscesses, and by Sevestre and Gaston in the joints in a case of polyarthritis complicating the disease.

It is not surprising, in the face of the observations of Piard and Akerman, that cases of polyarthritis in connection with perityphlitis may appear clinically much like rheumatic arthritis. There may be no definite local evidence of the original focus, possibly only a vague history of abdominal pain with vomiting. The swellings of the joints may be multiple, and disappear during life, the fever be lowered and pain relieved by salicylates, yet after death a gangrenous appendix and visceral abscesses may be found, pointing conclusively to the metastatic origin of the joint infection. Not only may there be effusion into the joints, but also into the tendon sheaths in their neighbourhood, and around the epiphyses of the bones. If we can be guided by Akerman's experimental results, the disappearance of the joint effusion during life may be looked upon as an evidence of the slight virulence of the *local* infections. If with this the *general* toxæmia be severe, then there will be death, but disappearance of the joint swellings prior to its occurrence ; if the general poisoning be not severe, then there will be recovery, with a condition of multiple arthritis simulating acute rheumatism. In a case of this kind which ended fatally, and in which the appendix was gangrenous, we have seen marked relief from the use of salicylates.

It is probable, therefore, that the arthritis occurring in connection with perityphlitis is usually of the nature of a pyæmic rather than a rheumatic affection, and this becomes the more probable if there is high irregular pyrexia, or if there are rigors.

That the condition should be liable to occur when the local indications of perityphlitis are slight, is in part, we suppose, explained as follows: If the attack is very severe, there is perforation, with either speedy death, or recovery after an immediate operation. If the attack is not so severe, but the local signs are definite, then, should unfavourable symptoms arise, a laparotomy is at once performed, and the metastases nipped, as it were, in the bud. If, however, the local signs are practically absent, and the history of the illness indefinite, then these metastases develop while there is doubt as to where the primary focus is to be found, or as to whether such a focus exists at all. It is probable also that in these cases there is an unusually rapid blood infection, rather than any great direct extension of the local suppuration.

This question of the exact nature of the arthritis is clearly one of practical moment, for if rheumatic, temporising measures might be employed, but if pyæmic, removal of the local focus is imperative. It is of some interest that just as this arthritis may closely resemble that of rheumatism, so may rheumatic arthritis sometimes resemble perityphlitis. Upon three occasions we have seen monarticular rheumatism of the right hip-joint in a child simulate this condition. The thigh is flexed, and the pain radiates over the right iliac fossa. In these days of active surgery the diagnosis is of course important, and usually quite easy. Other joints become affected, or the heart shows evidence of active rheumatism, indeed the knowledge of the possibility of this occurrence is usually sufficient to prevent any error. In conclusion, it appears to us that clinical evidence is, on the whole, against the rheumatic origin of the arthritis associated with perityphlitis.

REFERENCES

[1] Dr. G. A. Sutherland, "Appendicitis and Rheumatism," *Lancet*, August 24, 1895; *Edinburgh Hosp. Rep.*, 1895.

[2] Dr. Burney Yeo, "Rheumatic Perityphlitis," *Brit. Med. Jour.*, June 16, 1894.

[3] Sir James Grant, *New York Med. Rec.*, November 11, 1893, p. 609.

[4] Dr. Brazil, *Brit. Med. Jour.*, May 1895.

[5] Dr. A. Haig, *Brit. Med. Jour.*, June 30, 1894.

[6] Dr. Beverley Robinson, *New York Med. Rec.*, 1895, p. 375.

[7] In a recent letter Dr. Robinson expressed himself as convinced

from clinical observation of the rheumatic origin of some cases of appendicitis.

[8] E. Piard, "Des Suppurations ã distance dans l'appendicité," *Arch. gen. de Med.*, Paris, 1896, II.

[9] Akerman, "Lésions Osteomyélitiques," *Arch. de Med.*, exper. No. 3.

[10] Hodenphyl, "Ætiology of Appendicitis," *New York Med. Jour.*, 1893.

[11] Barbacci, *Centrl. und Allg. Path. et Path. Anat.*, October, 1893.

[12] Macaigne, *Le Bacterium Coli Commune, son role dans la Pathologie*, Paris, 1892.

PAPER NO. XXV

A FURTHER CONTRIBUTION TO THE STUDY OF RHEUMATISM. THE EXPERIMENTAL PRODUCTION OF APPENDICITIS BY THE INTRAVENOUS INOCULATION OF THE DIPLOCOCCUS

(Reprinted from the *Proceedings of the Royal Society of Medicine*, 1911, vol. v, Pathological section, pp. 18–29.)

From the Research Laboratories of University College Hospital and the Cancer Hospital Research Institute.

This paper records, we believe, the first examples of an experimental appendicitis produced by the diplococcus isolated from a lesion of acute rheumatism. Such results naturally revived the questions considered in the previous paper concerning the association of rheumatism and appendicitis, and although the greatest caution is needed in drawing conclusions from experimental investigations, lends support to the view that there may be some direct connection. Appendicitis from this standpoint becomes a symptom of various infections, including among these the rheumatic.

The experiment which by intravenous inoculation produces as the only obvious lesion of the entire length of the alimentary canal an appendicitis is a very striking one, and reminds us that the solitary lesion of appendicitis in man need not necessarily be the outcome of a local cause within the lumen of the tube, but may result from an infection gaining access from the peritoneal surface by the general blood stream. In this country this possibility, in spite of Kelynack's early work, has been somewhat overlooked, but Adrian's researches in Germany in 1902, *had stimulated this line of inquiry in that country, where a considerable literature has arisen around the question.*

THE first step in this communication is to indicate accurately the source of the infective agent with which our results were obtained.

A boy, aged 14, previously healthy and with a good family history, came to University College Hospital in August 1911,

suffering from a first attack of acute rheumatism of five days' duration. It commenced with pain in both knees and ankles, and later in the left shoulder. His temperature was 100.5° F., and pulse-rate 100 to the minute. Both knee-joints were tender and full of fluid, and the other joints named above were painful. For twenty-four hours an apical systolic murmur was faintly audible, but this disappeared, and the boy made a rapid and complete recovery. He was treated with salicylate of soda. The only point at all unusual in this case was the excess of fluid in both knee-joints, the right one being distended. Mr. C. E. Shattock, acting house physician, tapped this joint for us and a greenish fluid, which coagulated and contained some fibrinous shreds, was obtained. From this the diplococcus was isolated and grown in pure culture, and is the infective agent which we have used for the following experiments.

The animals used for experimentation were rabbits, and we would lay special stress upon the point that we used consistently for the first time young ones of some six to seven weeks of age. All the injections were made from bouillon cultures into the auricular veins.

The first animal injected with a large dose died of general pericarditis. The second was six weeks old and received ½ c.c. of a bouillon culture. Multiple arthritis followed and mucous diarrhœa, the animal dying from an intussusception of some days' duration. In passing we would comment upon this occurrence of acute intussusception in two animals as a sequel, and possibly a result, of the infection. A pure culture of the diplococcus taken from the joint of this animal was used for the third rabbit. This was seven weeks old, and was inoculated on September 2 with 1 c.c. of a bouillon culture. *Monarthritis* of the left knee-joint developed, with general illness and diarrhœa ; death occurred on the third day. The post-mortem showed *that for 1½ in. in the middle two-fourths of the appendix there was acute inflammation.* The left knee-joint showed the usual early synovitis. The liver showed fatty areas. The spleen was slightly enlarged and firm. The kidneys were not remarkable. There were no petechiæ and there was no post-mortem staining, the heart was not opened, but there was excess of fluid in the pericardial cavity. The diplococcus was recovered in pure culture from the left knee-joint and the heart's blood.

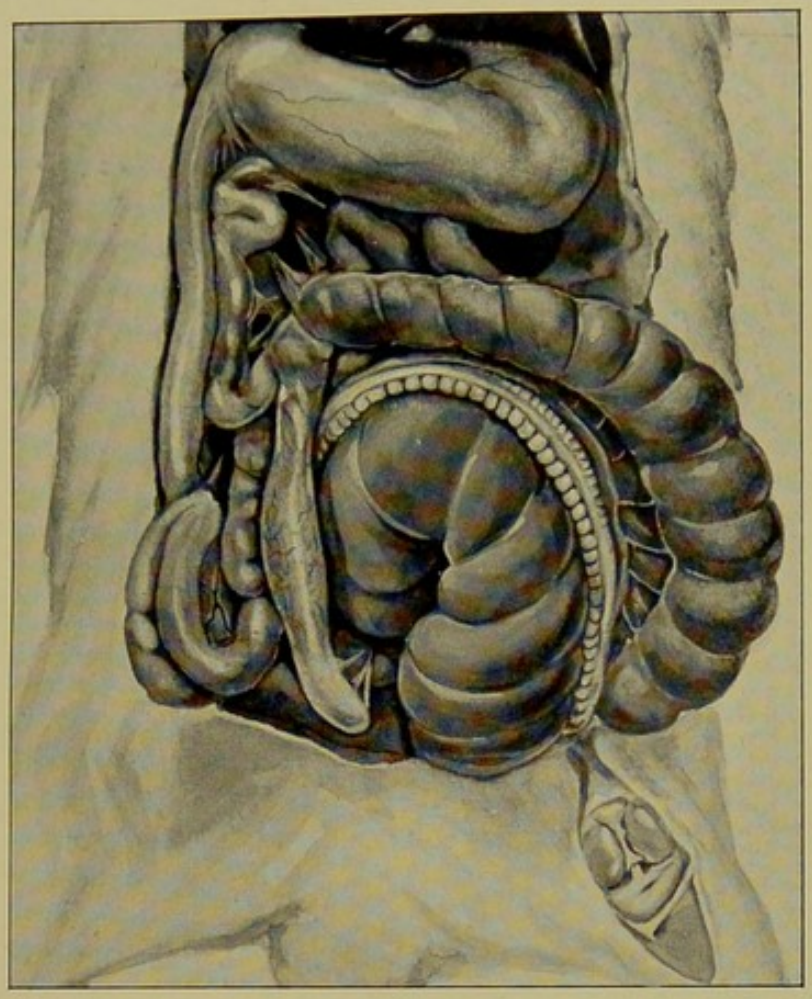


FIG. 88

Experimental appendicitis (rabbit). Abdomen opened, showing the swollen and inflamed appendix. The left knee-joint which was in a condition of acute arthritis, has been opened.

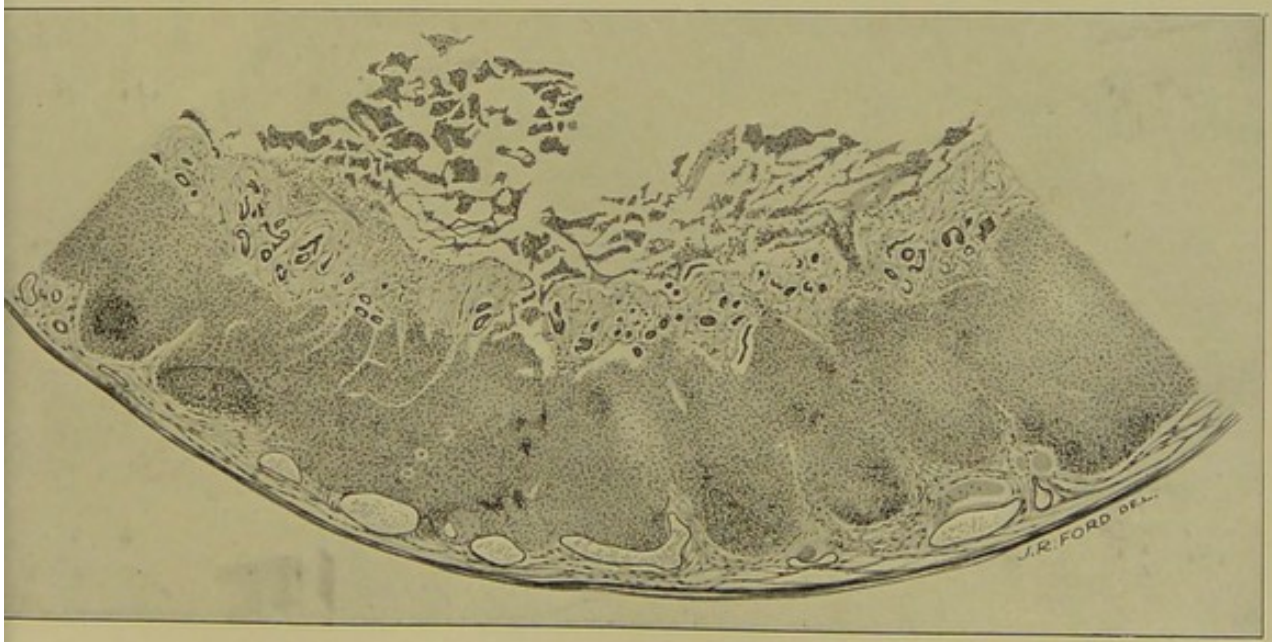


FIG. 89

Experimental appendicitis (rabbit). Section through the inflamed area of the appendix, showing: 1. Exudation in lumen. 2. Destruction of Lieberkühn's crypts. 3. Necrosis of lymphoid follicles. 4. Dilatation of blood-vessels at the base of the submucosa. *Cf.* Fig 98.

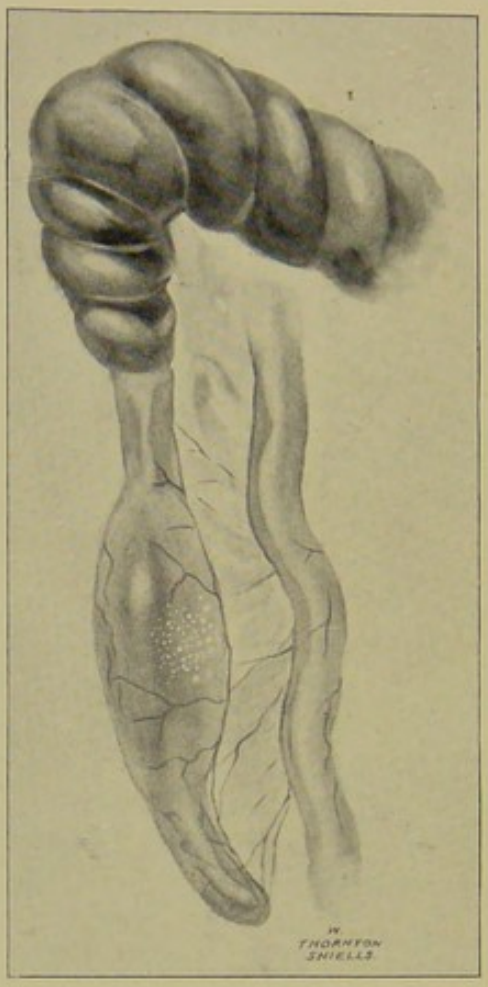


FIG. 90

Experimental appendicitis. A diagram showing ballooning of the appendix, the result of local infection of the wall by the diplococcus.

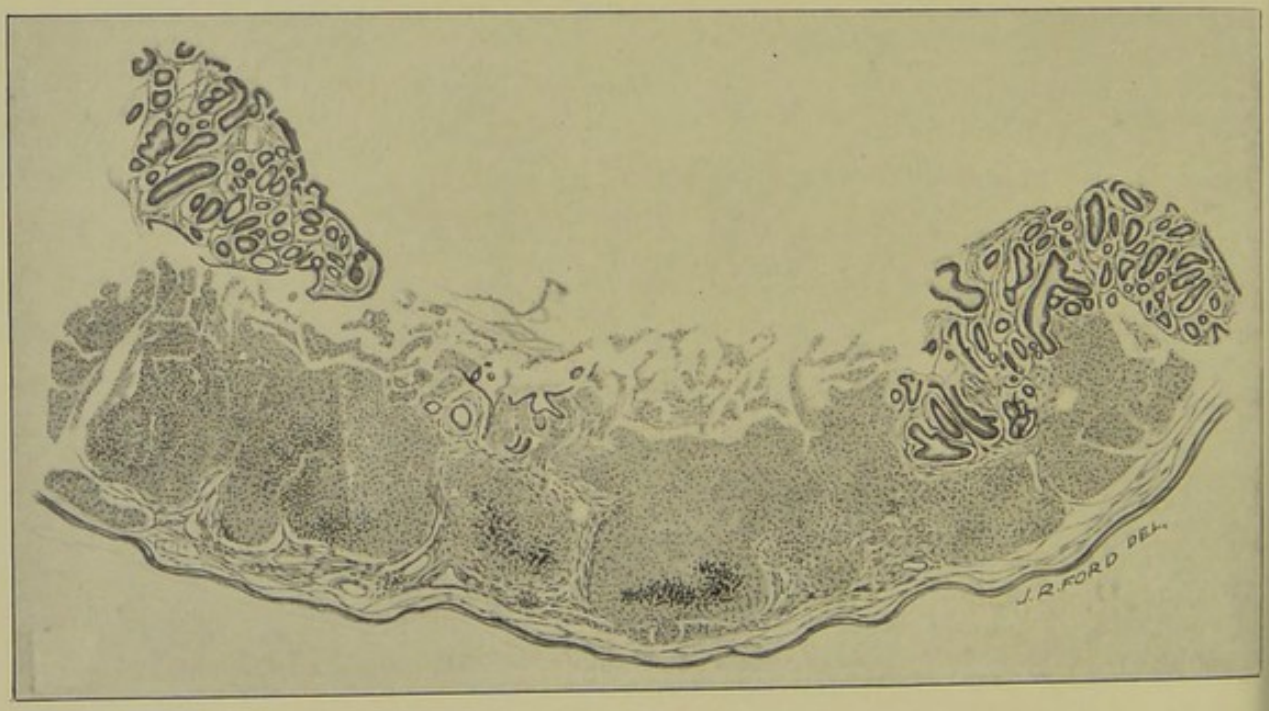


FIG. 91

Experimental appendicitis (rabbit). Section through the wall of the appendix showing the formation of an ulcer.

The appendix was clearly inflamed and the mucous membrane swollen and red. A small piece was excised for histological investigations.

The details of this histological examination are as follows: The muscular and serous coats of the bowel are healthy, but the mucous and submucous layers show extensive necrosis. There is destruction of Lieberkühn's glands and the lymphoid tissue. The basal vessels of the submucosa are engorged with blood, and numerous diplococci can be seen both in the vessels and in the tissues of the mucous and submucous coats. The Bacillus coli has invaded the necrotic area. Lastly, there is a slight fibrino-cellular exudation into the lumen of the gut. Although this was the third rabbit alluded to in this paper, four others had been inoculated and developed multiple arthritis without appendicitis. One more in this series, however, that is, the fourth mentioned here, developed in addition to multiple arthritis in both elbow-, knee- and carpal-joints, some diarrhœa and was killed when *in extremis* on the fifth day. *The middle two-fourths of the appendix* showed small opaque areas, deep seated in the substance of the wall, and this part was swollen and firm to the touch. The blood-vessels in this situation were engorged. On opening the appendix a mucoid fæcal-stained fluid escaped, and at one spot on the inner surface a reddened depressed area the size of a hemp seed was visible. The opaque areas seen from the external aspect were still more obvious from within; at the junction of the appendix with the cæcum there was an enlarged lymphatic gland, and there was excess of fluid in the peritoneal cavity. The spleen was slightly enlarged but not soft, the liver was dark and firm and the kidneys pale. The heart was dilated and full of blood; there was no pericarditis or endocarditis. The lungs were congested and there was excess of fluid in the pericardial cavity. A pure culture of the diplococcus was recovered from a knee-joint. The depressed area in the appendix proved to be an acute ulcer, the histology of which was as follows: The chief changes are visible in the mucous and submucous coats. These are of two kinds, in some places there is disappearance of the lymphoid tissue with a tendency to necrosis, in others a proliferation of the connective-tissue elements, pointing to the first stage towards a fibrosis. Diplococci were not demonstrated in the portion of the tissue

examined, in which reparative processes were just commencing. In the area of ulceration there is local necrosis of the mucosa and submucosa, with destruction of the epithelium of Lieberkühn's follicles and the lymphoid tissue. The muscular and serous coats are not involved and formed the base of the ulcer. The connective tissues bounding the necrotic area show commencing proliferation.

Another series of inoculations was made from the culture taken from the first rabbit which had suffered from acute appendicitis, and one of this series was killed when *in extremis* on the third day. During life arthritis of both knee-joints had shown itself and there was some diarrhœa with general illness, the result of the inoculation. On opening the abdomen a condition was observed which we must ask you to accept from our account, because in the process of preservation it could not be preserved. We have illustrated it by means of a diagram. The *middle two-fourths of the appendix* were ballooned and in the walls were small opaque areas not so extensive as in the preceding case, and situated chiefly along the mesenteric attachment. The viscera showed no noteworthy features and both knee-joints were in a condition of early arthritis. The diplococcus was recovered from one of these in pure culture. The histology of this condition shows the earliest stage of an infection by the blood stream. The first changes appear in the mucous and submucous layers, but chiefly in the lymphoid follicles of the latter. Small foci of polynuclear cells can be seen here and there surrounding the minute blood capillaries, and every stage of inflammatory change can be traced up to complete destruction of the normal tissue, ending either as necrosis or connective-tissue proliferation. Diplococci are visible in various stages of destruction within the phagocytic cells, according to the stage of inflammatory reaction.

The last series that have been inoculated consisted of three young rabbits seven weeks old, which were intravenously injected on October 6 with very small doses (0.25 c.c. and 0.1 c.c.) of a bouillon culture from the knee-joint of the preceding rabbit with appendicitis. All suffered from arthritis, and one from diarrhœa, and this one died on the ninth day. There was marked arthritis of the left carpal joint and slight of both knee-joints, the synovial membranes of which were red and congested. About ½ oz. of turbid fluid was removed from

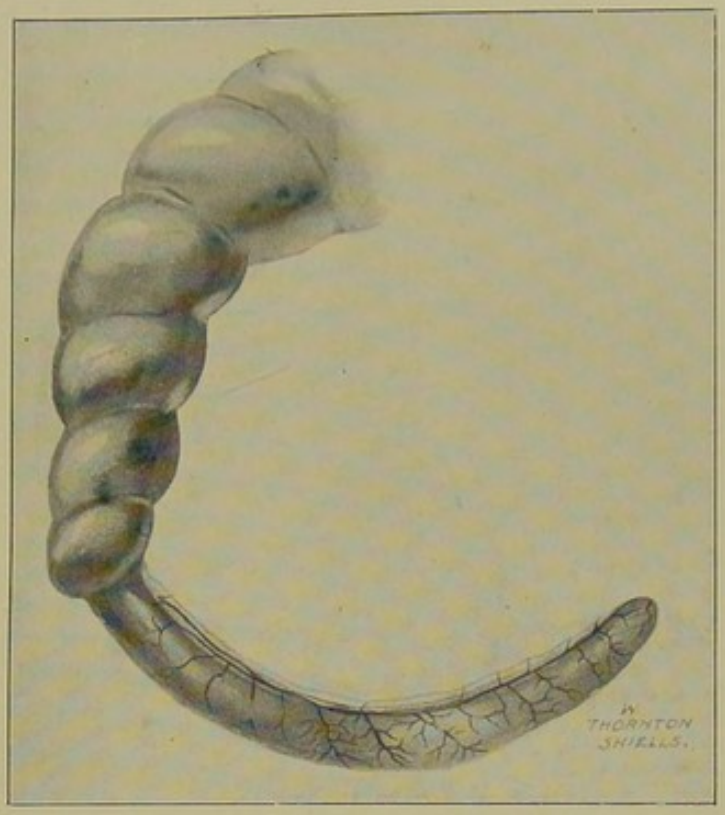


FIG. 92

The earliest visible change in experimental appendicitis (rabbit). About the middle third is seen a pale area surrounded by congested vessels : the pale area is the result of tissue necrosis.

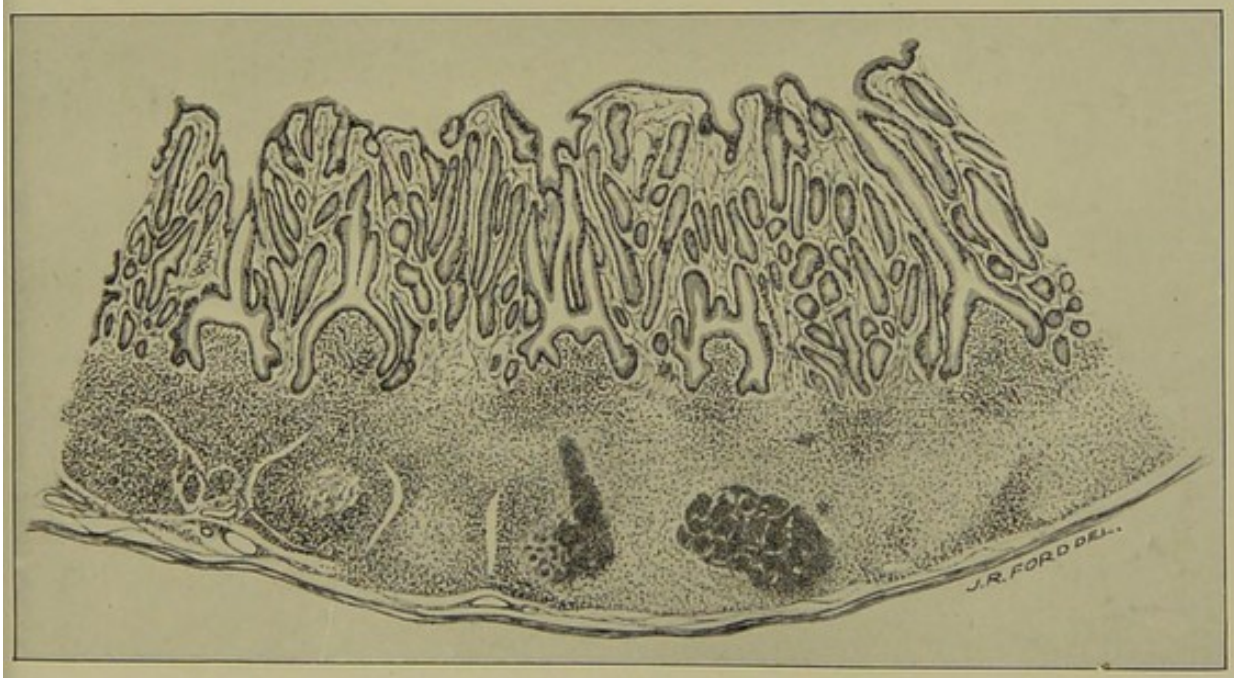


FIG. 93

Experimental appendicitis (rabbit). Section through the wall of the appendix under low magnification showing the early stage. Lieberkükn's crypts are not damaged, but areas of necrosis are visible in the lymphoid follicles of the submucosa.

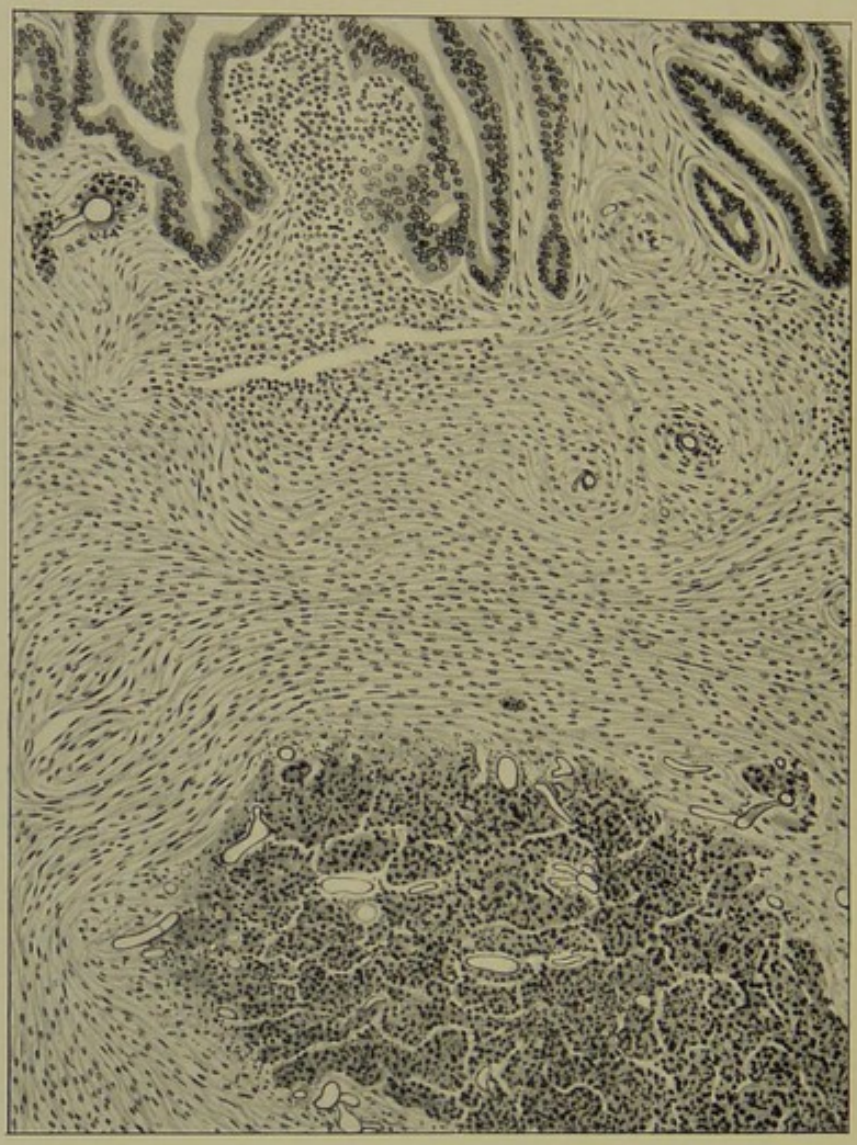


FIG. 94

Experimental appendicitis. Section through a part of the wall of the appendix, showing necrosis of lymphoid tissue and perivascular exudation.

the peritoneal cavity, and the serous membrane showed early inflammatory changes. The appendix at the junction of the *last fourth with the first three-fourths* showed an opaque area deeply seated in its walls. The blood-vessels were congested. As regards the other viscera there was no noticeable feature except that the spleen appeared to be unusually small. Cultures from the left carpal joint and peritoneal fluid gave a pure growth, and films also showed the diplococci. We would emphasise the absence of the *Bacillus coli* in the films and cultures of the peritoneal fluid. Thus it will be recognised that in this case, which had lasted nine days, some peritonitis had occurred and the living micrococci were present in the peritoneal fluid.

Summary

To summarise our histological results, we would point out the occurrence of (1) a very early appendicitis, (2) a very severe appendicitis, and (3) the formation of an ulcer as the result of a local deposit of the diplococcus intravenously injected. We would also express our belief that in human appendicitis, apart from the complicating event of a concretion which we know is not a constant occurrence—the histological changes might be well explained by our results. The early cases with their deposits in the submucosa and mucosa showing cell proliferation and little necrosis, might well, if they had been prolonged in duration, have produced sclerosis of the wall such as occurs in chronic human appendicitis. The acute case with much necrosis would represent the virulent human condition. Lastly, the ulcer, had it healed and been rather more extensive, would have produced the stricture so often seen in man.

The rapid destruction of the diplococci by the tissues is a most interesting event, fully bearing out our previous experiences as to this micrococcus, which have led us so repeatedly to explain the difficulty of its isolation during life.

The enlargement of the lymphatic gland at the base of the appendix is paralleled in human appendicitis.

In none of these cases or in the twenty-four rabbits inoculated in this research was there a single abscess in the viscera. In so far as these results are the outcome of infection with a

micro-organism obtained during life from rheumatic arthritis, and a micro-organism, too, capable of reproducing a similar arthritis, they are, we believe, a new contribution to the subject of experimental medicine and a new fact in the pathology of the important condition of appendicitis. If, however, we were to claim that the wider question of the possibility of appendicitis arising as a local result of a general blood infection had not been realised and experimentally investigated before, then we should do a gross injustice to others. Absolutely independent as these investigations of ours have been, we must refer to Adrian's paper published ten years ago upon the occurrence of appendicitis, both clinical and experimental, as a result of general infection. This author, in a masterly investigation, refers to this production of appendicitis in rabbits by the intravenous injection not only of streptococci, but also staphylococci, typhoid bacilli, pneumococci, and the *Bacillus coli*. In the investigation with the pneumococcus he demonstrated the micrococcus in the wall of the appendix, and his microscopic section of the inflamed appendix resulting from a streptococcus infection, the figure of which is in accord with the histological results that we have shown. He gave no details of the formation of an ulcer, or of another lesion such as arthritis, or of the condition of the peritoneal fluid, nor does he mention the source of the streptococcus, but these points are of secondary importance with regard to the general question with which his contribution was concerned.

In his paper Adrian gives many references to the work of others upon the general question of the origin of appendicitis from a general blood infection or local injury. Roux and Josué, Roger, Beauserrat, de Rouville, Gouget, and others have investigated in various ways upon this question and Adrian's paper in the *Mitteilungen aus den Grenzgebieten der Medizin und Chirugie*, 1901, vii, p. 407, reviews this work.

We would make the following concluding observations :

(1) There seems to us no doubt that in these cases acute appendicitis resulted directly from an intravenous inoculation of a diplococcus obtained during life from an acute rheumatic arthritis, and it appeals to us as interesting that it was the only obvious alimentary lesion, a point which Adrian noted in his cases.

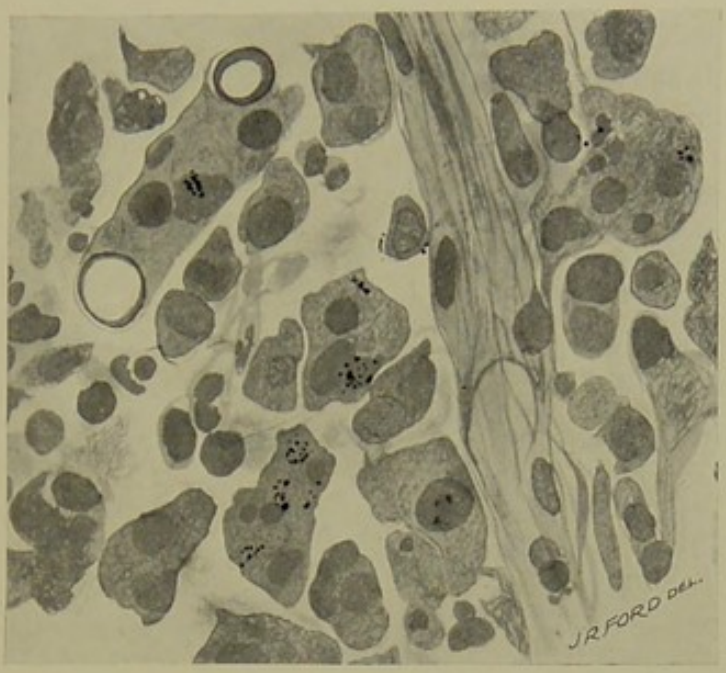


FIG. 95

Experimental appendicitis (rabbit). Section through the inflamed area showing destruction of the diplococci within the tissue-cells. *Cf.* Fig. 102.

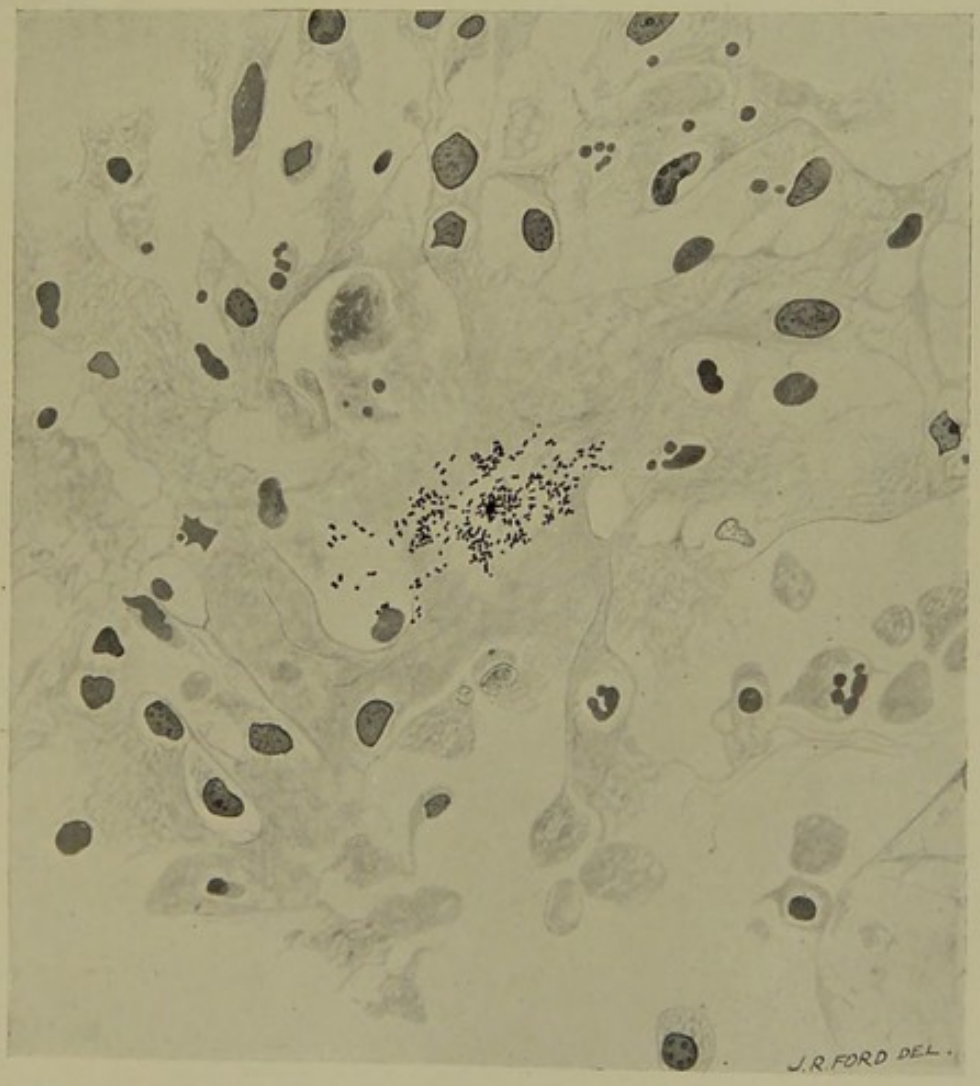


FIG. 96

Experimental appendicitis. Section through an inflamed area in the mucous membrane showing the diplococci.

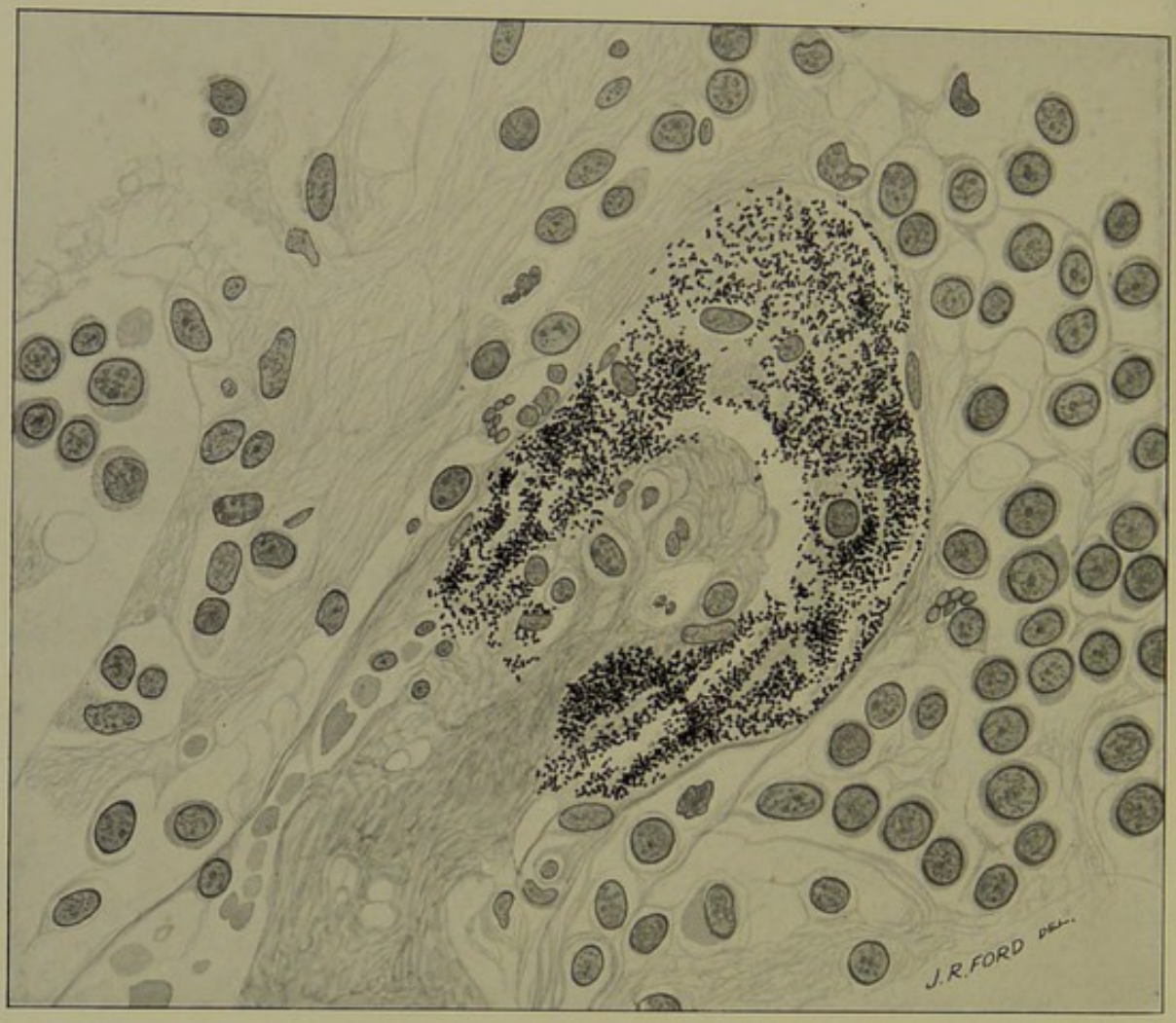


FIG. 97

Experimental appendicitis. Section showing diplococci in a blood-vessel of the submucosa.

(2) The conditions that were produced were of varying severity.

(3) In each case the animal was young ; heretofore, we have not observed such a condition in the older animals. This may, or may not, prove to be an accurate observation.

(4) The condition arises without the presence of any concretion or foreign body in the appendix and commences deep in the wall of the appendix. This militates, in our opinion, against the view held by Aschoff that in human appendicitis this disease starts within the lumen of the appendix.

(5) It is interesting that the middle part of the length of the appendix is affected, a position in which a stricture is so often found in man.

(6) In one case early peritonitis with living diplococci in the peritoneal fluid occurred, although there was no perforation—a point of much importance in its bearing upon the pathology of human appendicitis.

(7) The ballooning of the affected area of the appendix in one case suggests the probability that in man some such loss of tone favours stagnation of secretions and contents, and the formation of a concretion.

(8) The association of arthritis, mucous diarrhœa and appendicitis is of interest in its bearing upon the difficult question of auto-intoxication from the bowel in the human subject as a cause of arthritis. It suggests that rather than this being the primary factor, the probability is that all the lesions may be the result of some primary cause circulating in the blood stream and determining to these various positions.

(9) We do not assert for one moment that the only cause of appendicitis is this diplococcus. Adrian's investigations and those of others are sufficient evidence, quite apart from clinical experience, to prevent us falling into this error.

(10) Whether or not these results favour the widely held view of a relationship between acute rheumatism and appendicitis must depend upon the significance that is attached to this diplococcus and the degree of parallelism that exists between human disease and experimental infection.

PAPER NO. XXVI

A FURTHER CONTRIBUTION TO THE STUDY OF THE ÆTIOLOGY OF APPENDICITIS AS A RESULT OF A BLOOD INFECTION; WITH PARTICULAR REFERENCE TO THE TONSILS AS THE PRIMARY SEAT OF INFECTION

(Reprinted from the *Lancet*, August 17, 1912)

This short paper brings again into prominence the possibility of appendicitis arising as a blood infection from a distant focus. In this case the primary lesion was apparently a streptococcal tonsillitis. The illustrations of this paper hitherto unpublished, should be compared with those in the preceding one, and the similarity of the human and experimental lesions will be seen to be most striking.

In this communication we shall attempt to advance toward a practical issue the suggestions that we put forward as a result of some experimental investigations reported in the *Lancet* last year.[1]

1. The Case

The case upon which our new facts are based was that of a girl, aged 15 years, who was taken to University College Hospital on June 2, 1912, suffering from a first attack of appendicitis. The illness was a very definite, but not unusually severe one, and the diagnosis was particularly easy because in addition to the ordinary signs of the disease the enlarged and tender appendix could be easily felt through the abdominal wall. The duration of the attack was forty-eight hours. To Mr. H. C. G. Pedler, the house physician, we were indebted for the interesting and valuable observation that the right tonsil was inflamed, and in some of the crypts a follicular deposit was evident. No complaint of a sore-throat had

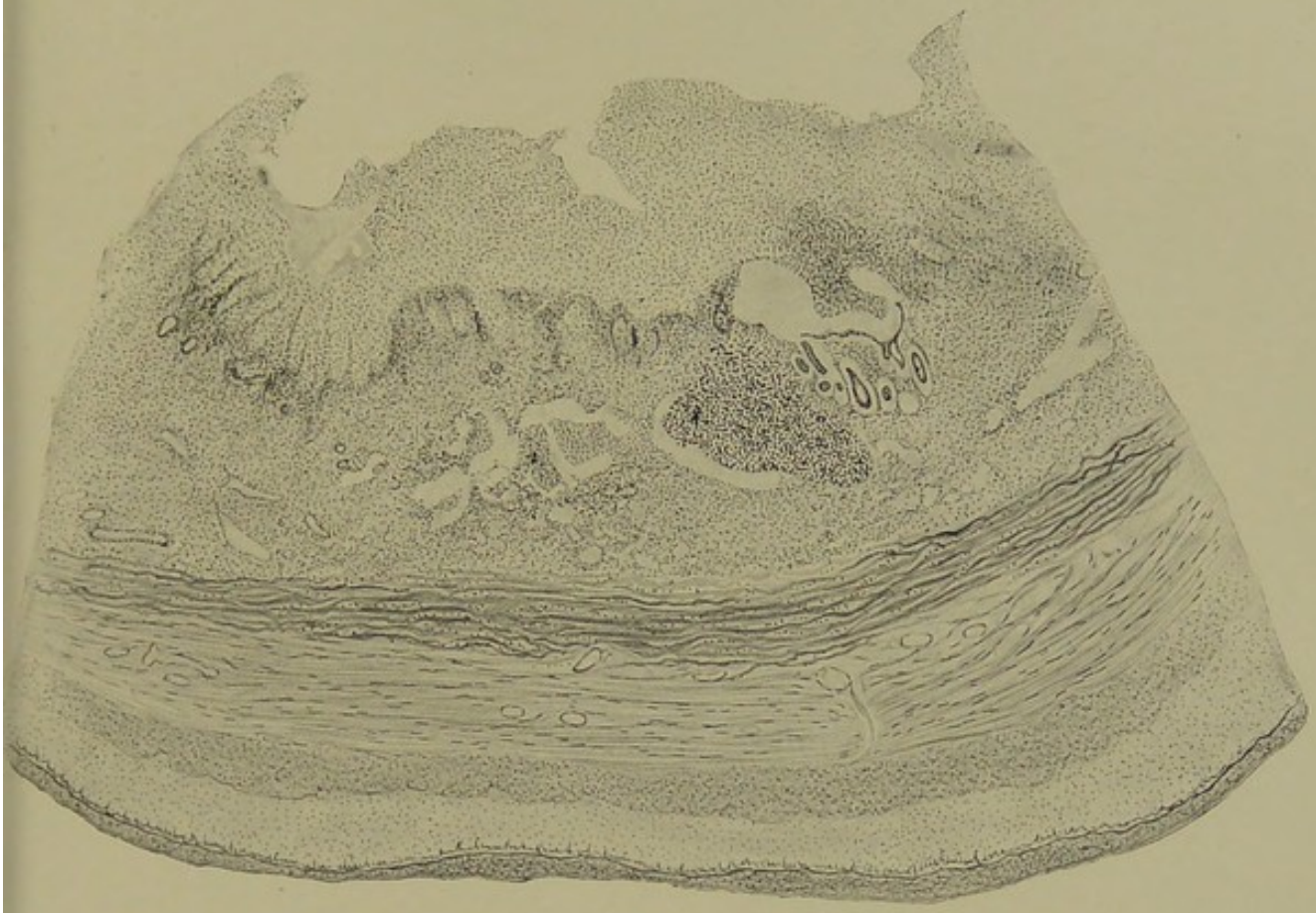


FIG. 98

Section of the acutely inflamed appendix (human), under a low power (*cf.* Fig. 89), showing: 1. Exudation in lumen. 2. Destruction of Lieberkükn's crypts. 3. Necrosis of lymphoid follicles. 4. Fibrino-cellular exudation at the base of the submucosa. 5. The inflamed serous membrane.

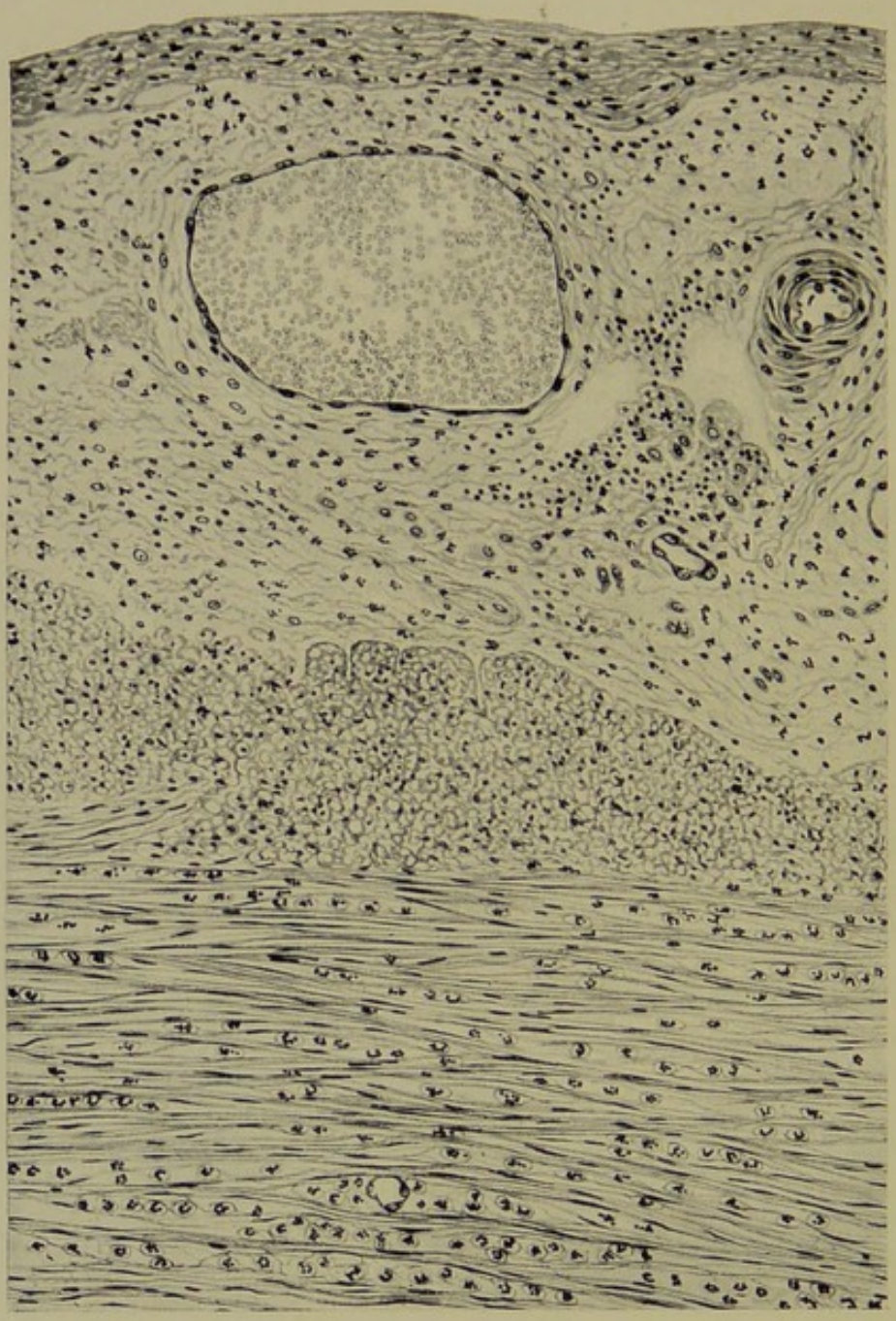


FIG. 99

Another part of the same section shown in the preceding figure under a higher power, showing infiltration of the muscular coats with inflammatory exudation and dilatation of the vessels, with fibrino-cellular exudation in the serous membrane.

been made by the patient, who was no doubt suffering far more from abdominal pain. Mr. Raymond Johnson operated at once and removed a large and swollen appendix covered with fibrino-plastic exudation. There was neither gangrene nor perforation, and there was no concretion. The patient made an uninterrupted recovery. There was no previous history of any serious illness.

2. The Investigation

While under the anæsthetic a culture was taken from the right tonsil, and the appendix was placed in a sterile tube.

(*a*) The bouillon culture from the throat showed mainly strepto-diplococci, but also a few staphylococci and an occasional bacillus. There was no difficulty in isolating the diplococcus from the culture.

(*b*) Cultures from the appendix made by smearing the exudate upon agar showed mainly the bacillus coli, but also some colonies of strepto-diplococci.

(*c*) Cultures from the sanious fluid which had exuded from the appendix after it had remained a few hours in the sterile tube at room temperature, and which had been then withdrawn and incubated in a Pasteur pipette, gave a pure culture of strepto-diplococci.

(*d*) Some of the sanious fluid inoculated upon agar and into bouillon showed strepto-diplococci, but a predominance of the bacillus coli.

These results with the sanious fluid are of interest because they bear out our experience that in media such as bouillon, devoid of immune factors, the more saprophytic coli organisms rapidly get the upper hand, but in the blood serum the more pathogenic organism grows the more readily. This point as to the importance of serum Kretz had already dwelt upon in his paper.[2]

The diplococci from the throat and from the sanious fluid appeared to us morphologically and in cultural characters identical.

A. *Experimental results with the culture from the throat.* The diplococcus produced arthritis with the usual accompanying symptoms in the rabbits intravenously inoculated and was again recovered in pure culture from the arthritic exudations. Later investigations have resulted in the production of malignant endocarditis with infarctions in the spleen and kidneys.

B. *Experimental results with cultures from the sanious fluid.* Two groups of investigations were made: (1) Six adult rabbits were inoculated intravenously with subcultures in bouillon with negative result. This loss of virulence in bouillon is a frequent event in the cultivation of micrococci of the streptococcal group. (2) Six young rabbits of six weeks of age were inoculated from subcultures on blood agar. Of these animals the first suffered from malaise and diarrhœa for three days and on the fourth developed arthritis of the right shoulder-joint. It was killed on the eighth day. The diplococcus was recovered from the inflamed joint. The spleen was small and the other organs were healthy. The second animal developed arthritis of both knee-joints on the third day with fever and malaise. It was killed on the fifth day. The post-mortem examination showed arthritis and appendicitis. The appendix showed the middle third as the injured part, and there were necrotic areas in the deeper layers of the wall of the appendix precisely similar to those detailed and illustrated by us in our paper read before the Pathological Section of the Royal Society of Medicine in October 1911. The diplococcus was recovered in pure culture from the joints. The third rabbit developed arthritis of the left knee-joint on the third day and was killed on the fifth; save for the arthritis it was apparently healthy. The fourth rabbit, after transient malaise, recovered without any local lesion. The fifth rabbit developed arthritis of the right knee-joint on the third day. The sixth rabbit developed multiple arthritis and was killed on the fifth day. Thus five out of the six rabbits developed arthritis and one of these in addition appendicitis.[3]

Pathological Investigations

The experimental appendicitis needs no further description, for it resembled precisely the condition which we fully described and illustrated in 1911.

The appendix, however, from the patient deserves some detail in description. Sections showed an acute diffuse change mainly affecting the submucous and mucous coats and the serous covering of the bowel. The submucous and mucous coats were in a state of acute necrosis, the result of minute hæmorrhages from and thrombosis of the vessels in the sub-

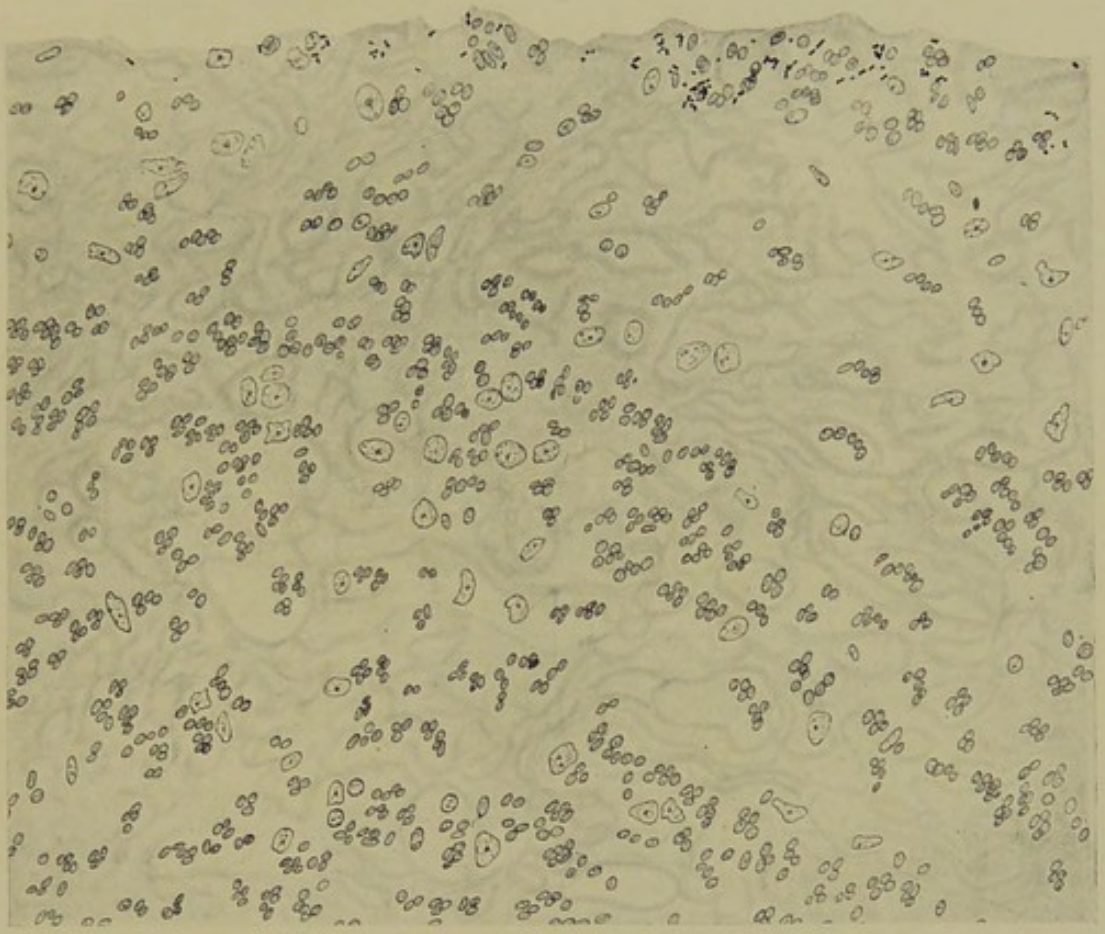


FIG. 100

Human appendicitis. Section through the serous membrane, showing diplococci and inflammatory exudation. (Zeiss, obj. 3 mm., apo. oc. 12.)

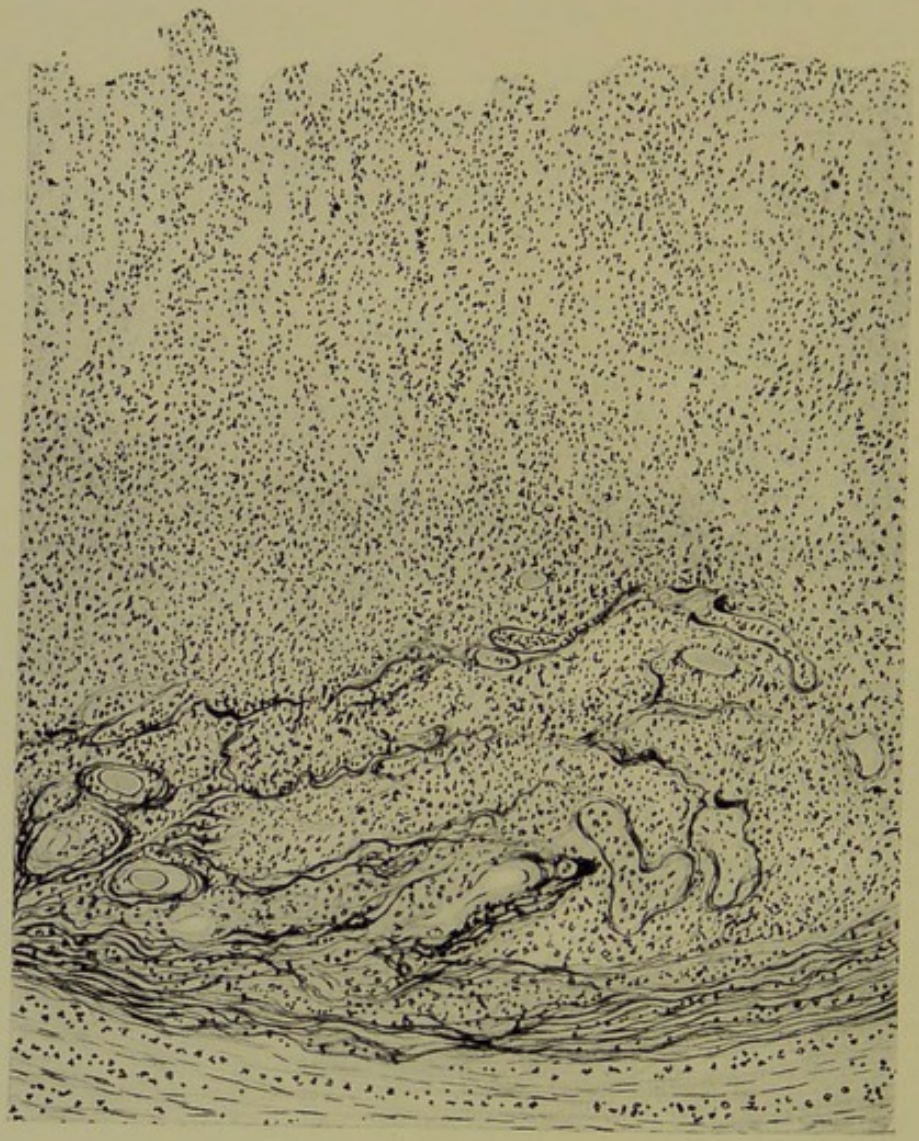


FIG. 101

A part of the same section shown in Fig. 98 under higher magnification, showing necrosis of the mucous membrane and thrombosis of vessels with fibrino-cellular exudation in the submucosa.

mucosa. A fibrino-cellular exudation infiltrated the submucous coat, in which the lymphoid tissue was almost completely destroyed. The mucous membrane was infiltrated with inflammatory cells, and there was almost complete destruction of its epithelial covering and of Lieberkühn's glands, only a slight trace of the deeper crypts being visible. The muscular coat was also infiltrated with inflammatory cells and the greatly swollen serous layer was œdematous and infiltrated with fibrino-cellular exudation. Diplococci were demonstrated in the submucous and mucous membranes, but were most numerous and easily demonstrated in the serous membrane. The bacillus coli had invaded the necrotic tissue and serous covering of the bowel. The condition of this human appendix was a counterpart of that found in the rabbits with appendicitis, as illustrated by us last year.

We think that this investigation brings us a step forward in the study of the ætiology of appendicitis. Since Kelynack [4] in 1893 directed our attention to the relation of tonsillar inflammation to appendicitis many German investigators have devoted much attention to the point. Our earlier paper showed that in young rabbits a micrococcus which we look upon as the exciting cause of acute rheumatism could produce a local lesion in the appendix by direct blood infection, and bearing in mind the importance of tonsillar inflammation in rheumatism those results naturally strengthened the view put forward by Kelynack. This investigation takes us forward, because it would seem beyond reasonable doubt that the diplococcus in the tonsil and in the sanious fluid from the appendix were identical in nature and the cause of the lesions in the human throat and appendix and also of those in the appendix and joints of the rabbits. In other words, it seems to prove almost conclusively that *a cause of appendicitis may be a streptococcal invasion through the blood stream from a follicular tonsillitis.*

REFERENCES

[1] *Lancet*, October 28, 1911, p. 1189.

[2] "Ueber die Ætiologie der Appendizitis, Verhandlungen der Deutschen pathologischen Gesellschaft," April 1910.

[3] A seventh rabbit developed arthritis and appendicitis after the publication of this paper.

[4] "The Pathology of the Vermiform Appendix"; London, H. K. Lewis, 1893.

PAPER NO. XXVII

OBSERVATIONS UPON APPENDICITIS BASED UPON A COMPARATIVE STUDY OF THE MORBID ANATOMY IN THE HUMAN AND EXPERIMENTAL DISEASE

APRIL 1913

In this paper the method adopted for isolating the streptococcus from cases of streptococcal appendicitis is detailed, and a further study of the morbid changes in recurrent human appendicitis has been added which supports the view that in such cases the cause is an infection attacking the organ from the general blood stream. Some general observations are added upon the pathology of the disease.

SINCE our papers published in 1911 and 1912, upon experimental appendicitis produced by a blood infection we have investigated more closely the morbid anatomy of the disease in man with the object of comparing the lesions with those produced by experiment. In this way we hoped to throw some more light upon the origin of the disease in man as the outcome of a blood infection rather than of a direct invasion by micrococci from within the lumen, or of injury. A very interesting and valuable monograph by Kretz has convinced us that in Germany much attention has been directed to this subject. In this country, however, the published writings of more recent date have paid but little attention to this method of origin.

Quite apart from the possible rheumatic causation of appendicitis it is clear that if the disease arises by infection from the general blood stream such hypothetical causes as faults in common articles of diet, sedentary habits and constipation, and foreign bodies must take a very secondary position. On the other hand, if the research recorded in the preceding papers should meet with further support, and we

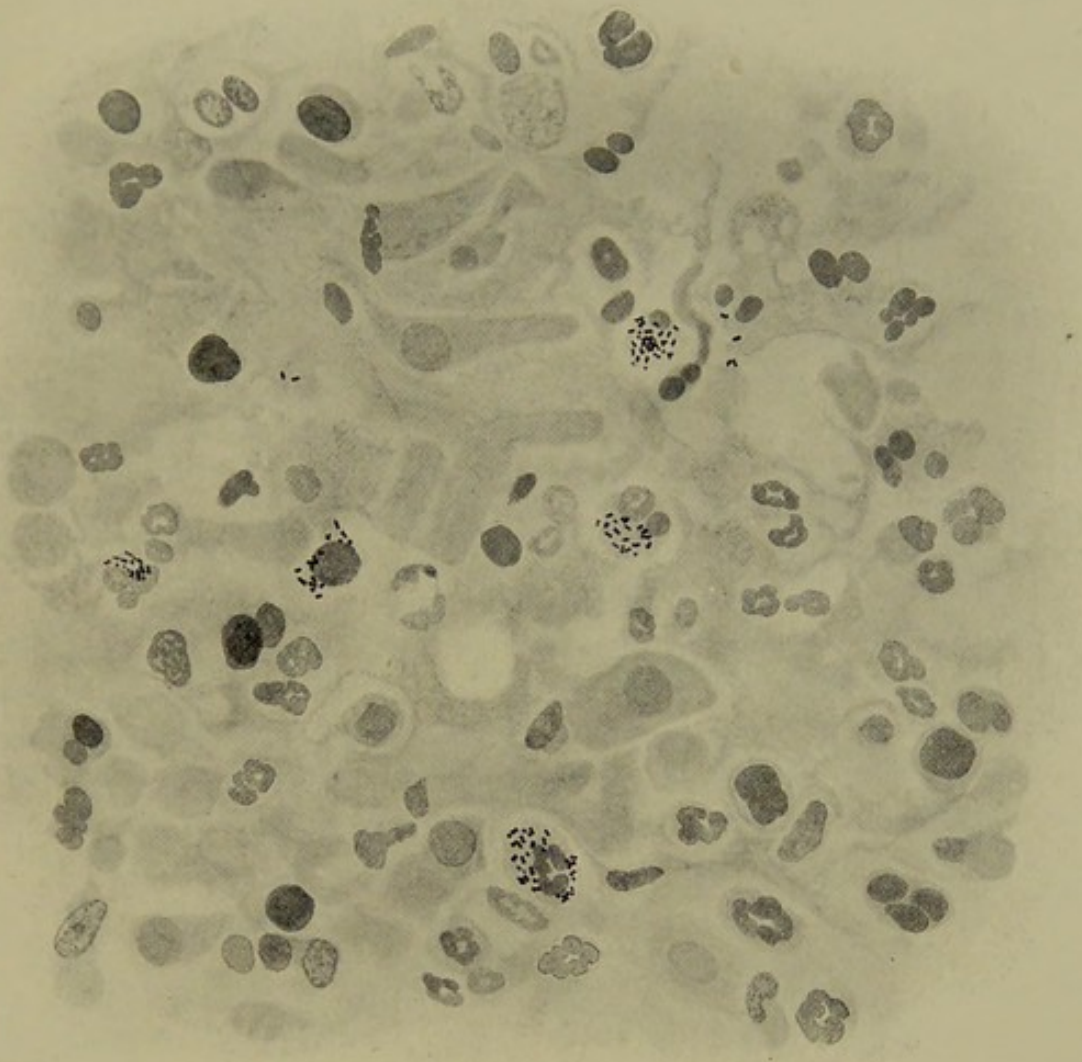


FIG. 102

Human appendicitis. Section through the submucosa showing destruction of diplococci in the phagocytes. (*Cf.* Experimental appendicitis, Fig. 95.) (Zeiss, obj. 3 mm., Apo. oc. 12.)

may add that in Germany many clinical observers, for example, Braun, Kretz, Krauss and Albrecht, attach the greatest importance to tonsillar infection, it is clear that all causes encouraging angina faucium would favour its incidence.

It would be premature to attempt to give a decided opinion upon the *rôle* of a tonsillar infection with the amount of exact evidence before us, but it is an interesting thought arising out of this possibility as to whether the increase in the disease which some are confident has occurred in recent years may not be dependent upon the great wave of influenza, an affection which so frequently commences with a sore throat. Some authorities, such as Lexer, Klenk and Friedjüng, although not prepared to admit a tonsillar infection in the sporadic cases are inclined to this when small epidemics have arisen ; and it is clear that in the future a careful consideration of the whole subject is worthy of close attention in this country. We would add in agreement with others that it should be remembered that the abdominal symptoms in appendicitis are often so severe as to make the patient forgetful of any previous sore throat of slight severity, and the paramount importance of the abdominal diagnosis distracts the attention of the medical man from what might well seem a trivial occurrence.

No one, we believe, would for a moment accept that the ætiology of appendicitis was to be explained as invariably the result of infection from the tonsils, for it is certain that in many cases no convincing evidence of such an infection is forthcoming, and although there is no theoretical need for the tonsils to be grossly inflamed in order to allow of such infection we should naturally hesitate to assume this source without some decided evidence in its favour.

At this point we would emphasise a difficulty in the investigation of the bacteriology of appendicitis, which not only baffled us for many months, but which is a very real one. The isolation of the micro-organisms is an undertaking full of difficulty and involving much labour because the bacillus coli quickly overgrows the streptococci which are so often the pathogenic cause.

We do not affirm that the bacillus coli may not be a cause of appendicitis, but we are of opinion that it is more usually a saprophyte which bewilders us by overgrowing our culture media. On this account we found it necessary to adopt a

special technique of the following nature. Our material has consisted of appendices obtained directly after removal by the surgeon. In the amputation the efferent lymphatics which drain from the mucous and serous coats into the mesentery are cut across, and we receive the appendix into a sterilised tube containing no culture medium. This we keep in the cool for some hours. The fluid oozing out is blood stained and collects at the bottom of the tube. Then this fluid is withdrawn in a Pasteur pipette, the end of which is sealed off in the flame, and incubated for twelve to twenty-four hours at the body temperature. If the case is an early one, the pathogenic agent is found sometimes in pure culture, sometimes with a poor growth of the bacillus coli from which it can be separated with comparative ease.

It was extremely interesting to us to find that Kretz had in his monograph suggested that a fluid of this kind might be the best medium.

All our later experiences have pointed to a streptococcus as the most frequent cause of appendicitis, and it is with this that we have produced experimental results. Further the streptococcus is extremely likely to produce polyarthritis in rabbits, in fact this result in young rabbits (the only ones in which, so far, we have produced appendicitis) has been almost constant. Endocarditis has, however, also resulted.

These experiences have borne out the results of other investigators in so far that they also have frequently isolated a streptococcus, and they have also extended them by completing the experimental evidence which had been previously incomplete. Other micrococci have been isolated as, for example, pneumococci and staphylococci, and twelve years ago Adrian demonstrated that appendicitis might be produced experimentally by intravenous inoculation of rabbits with various micrococci.

The question arises, and has not yet been answered, as to the nature of these streptococci which would seem to be the most frequently occurring infection.

Our first paper in which the diplococcus rheumaticus was isolated from the inflamed knee-joint during life makes it reasonable to entertain the view that among these streptococci the rheumatic infection may have a place. If then, in the future, among the causes of appendicitis acute rheumatism

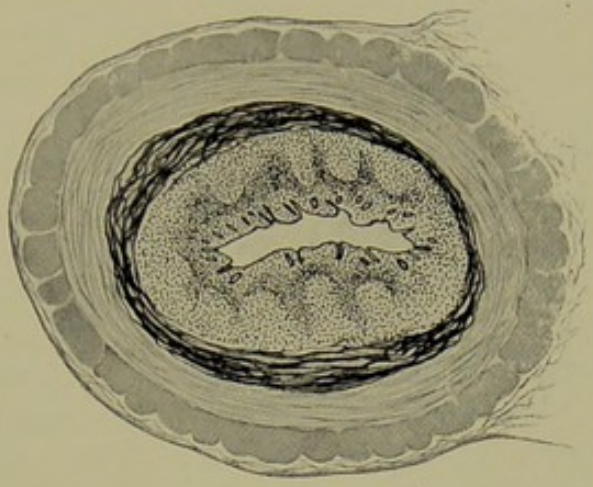


FIG. 103A

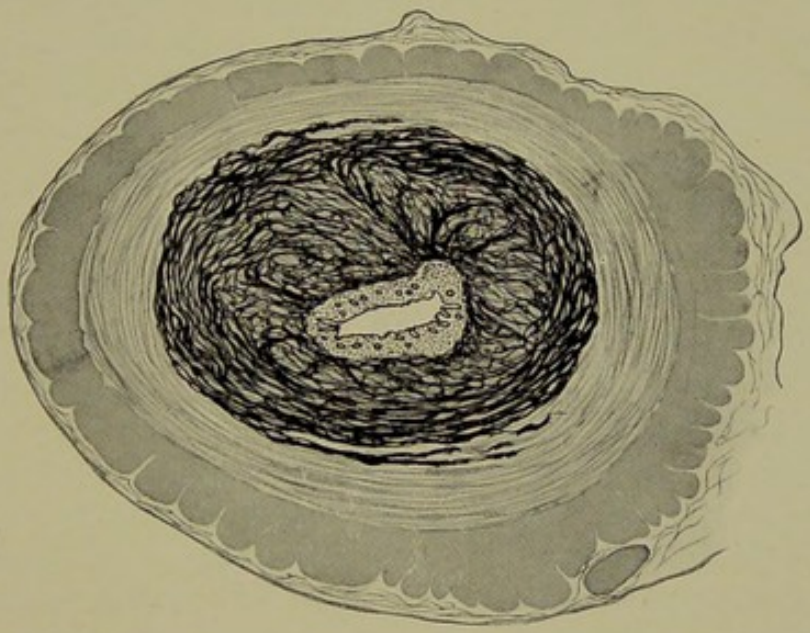


FIG. 103B

Transverse sections of two appendices (human). These semi-diagrammatic drawings were made under low magnification. Fig. 103A was taken from a normal appendix. Fig. 103B is from a case of recurrent appendicitis in a man aged 28; perforation occurred in the last attack. Showing the destruction of the deeper parts of Lieberkühn's follicles and the lymphoid crypts of the submucosa which are replaced by fibrous-tissue formation. There is also considerable thickening of the serous membrane.

should be generally accepted, it would be a point for consideration whether the rheumatic form showed any characters that served to differentiate it wholly or partially from the other forms.

In order to prove the existence of "a rheumatic appendicitis" much investigation over a long period of time will be necessary. The position to be aimed at is clear enough. We need to show on clinical evidence a connection between the two diseases and to demonstrate a common cause. In addition to this we require to be able to produce the disease in animals with the infective agent, and to show that the morbid changes in the human and animal tissues are of a like nature.

At the present moment the definite statement may be made that if there is a rheumatic appendicitis it is not a lesion which is often met with in the general acute disease in childhood. We have no doubt as to the association of arthritis and morbus cordis in rheumatism or of chorea and arthritis, or again of chorea and morbus cordis, but of appendicitis and these lesions experience tells a very different tale. If, then, an appendicitis is rheumatic it must be considered one of the rarer manifestations, or a manifestation the occurrence of which points to an unusual incidence on the part of the infection dependent possibly upon some individual peculiarity. We have convinced ourselves in the last ten years that some explanation of this nature is essential if a rheumatic form actually exists. So strong was our conviction upon this point that the experimental production of the disease came to us as a complete surprise, and we do not for the moment lose sight of the fact that great caution is needed in applying the results of experiment to human pathology. Nevertheless, as is so often the case in research, since the publication of our results we have had examples of the occurrence of an appendicitis apparently of rheumatic origin brought to our notice, and we have no right to ignore the fact that for many years various writers have held this view of its origin, Kelynack, Kretz, Beverley Robinson and Alexander Haig among others, or to forget that individual experience is at the best very limited. An unprejudiced study of this question is, we feel, deserving of attention, and there can be but little doubt that it is one which can eventually be settled. This is the more to be desired because the abdominal manifestations of rheumatism

have not met with much attention, and the work in Germany and our own results upon tonsillitis give a new impetus to further inquiry.

The form of appendicitis which would first attract the attention of the investigator is the relapsing one, for rheumatism is essentially a disease of that nature, and it is rational to postulate that such a process as we see every day occurring in the mitral valve might also occur in the appendix.

It will not escape the reader that the lesions that we have illustrated in the human and animal appendices are strikingly similar, the plates that are given in the two previous papers are most convincing upon this point. We see the diplococci in the tissues and their destruction in the walls of the appendix. The necrosis, the sero-fibrinous exudation, the vascular dilatation and thrombosis, the leucocytic infiltration and the formation of an ulcer. A study of relapsing appendicitis in man has enabled us to show the perivascular fibrosis and replacement of essential tissues by scar formation, a change common to many infections but most conspicuous in rheumatism on account of the rarity of suppuration and the great resistance to the disease. Further, a study of the human appendix shows us with increased certainty that the disease is more usually the result of a blood infection than of a local invasion of tissues from some primary cause within the lumen.

It is only reasonable to suppose that secondary factors may arise within the lumen when once the organ has been diseased, which lead to further injuries. The inflamed mucous membrane produces an exudation which, becomes mixed with the contents of the bowel and when inspissated develops into a concretion which, just as a gall-stone in the gall-bladder, may then in turn produce injury and inflammation. The appendix itself may become extraordinarily thickened and rigid from repeated subacute attacks of infection, and such a structure must be liable to injury from blows or sudden strains, particularly as the disease is exceedingly frequent at the athletic age. Again, if the inflammation is severe but localised a contraction of the lumen of the tube at that spot is to be expected, and behind this stricture pent up contents are very likely to become harmful. The muscular tissue which must surely serve some purpose in emptying the contents in health are often severely damaged as our

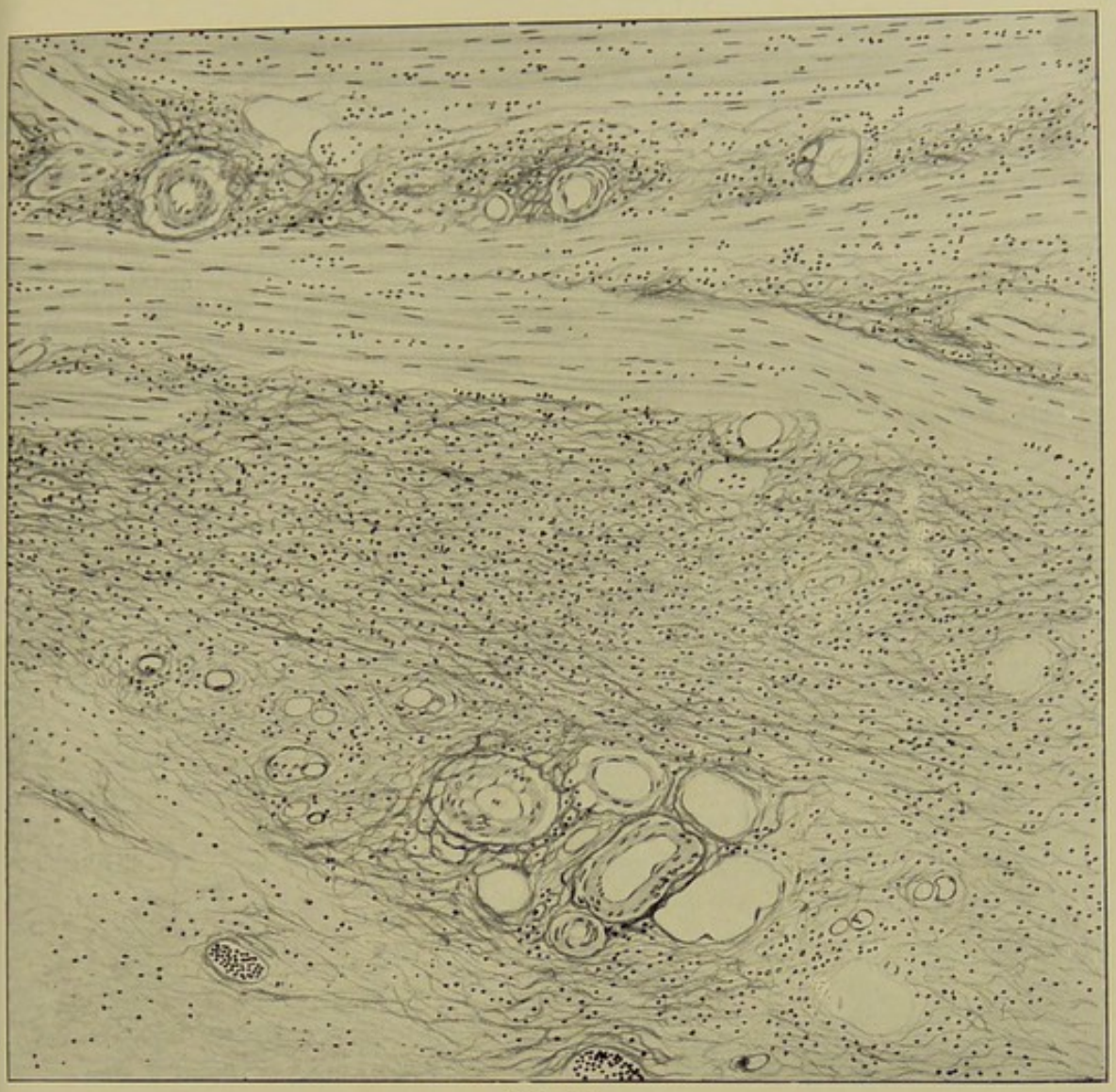


FIG. 104

Recurrent appendicitis (human). Section of the submucosa and inner muscular coat under higher magnification, illustrating perivascular fibrosis with infiltration of the muscular coat by the fibrous elements, the result of previous inflammation, together with leucocytic infiltration the result of the recent attack.

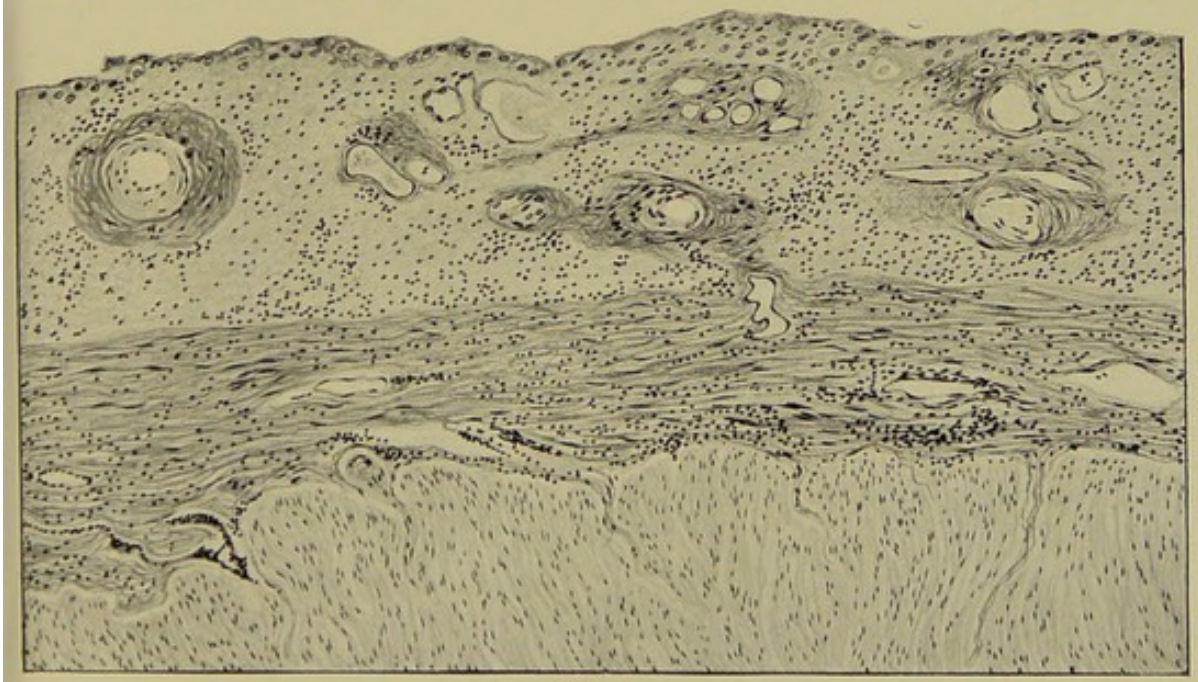


FIG. 105

Recurrent appendicitis (human). Section of the outer muscular coat and serous membrane under the same magnification as the preceding, showing perivascular fibrosis, the result of previous inflammation, together with leucocytic infiltration the result of the recent attack.

illustrations clearly show, and this damage will result in a tendency to the stasis of the contents within the lumen.

It is, then, evident that the problem of appendicitis is not a simple one. We do not suppose that even if the cause of any particular case be rheumatism that the final developments will be necessarily uncomplicated by the secondary factors described above, and the introduction of septic infection as a complication is one obvious probability. We would draw attention to the remarkable and undoubted fact that the intravenous injection of the diplococcus in the rabbit will produce a solitary ulcer in the appendix. It is, perhaps, one of the most remarkable experimental results we have ever seen, and it throws a very interesting light upon the pathology of intestinal ulceration in general, opening our minds to receive new facts upon the occurrence of gastric and duodenal ulceration in man.

The amount of progress that we have made upon the subject of appendicitis is, we admit, only small, but we believe, setting aside all question of the rheumatic origin, we have put forward and illustrated a view of the pathology of this important disease, or more correctly symptom of disease, which the future will show, explains its nature more clearly and more correctly than any hitherto favoured in this country. In brief our view is, that probably the great majority of cases of appendicitis are primarily the results of some infection—and particularly a streptococcal one—gaining access to the organ by the blood stream.

PART III

A STUDY OF ACUTE RHEUMATISM BASED UPON THE RESULTS OF THE PREVIOUS RESEARCHES

1. THE ÆTIOLOGY AND PATHOLOGY
2. SYMPTOMATOLOGY
3. DIAGNOSIS AND PROGNOSIS
4. TREATMENT
5. PREVENTION

THE ÆTIOLOGY AND PATHOLOGY

We shall attempt in this article to consider the disease termed "acute rheumatism" by the light of the preceding investigations, indicating their bearing upon the ætiology and pathology, symptoms, diagnosis, prognosis and treatment. In writing this paper we realise the inadequacy of the terms "acute rheumatism" and "rheumatic fever," but present usage has prevented us from abandoning them and employing as we should prefer the general term rheumatism.

(*a*) The Ætiology

The first step is a consideration of the older explanations of the causation and the part that they take in the evolution of the present position of the question. It is not to be supposed that the suggestions put forward by earlier writers, crippled though they were by limitations in methods of inquiry, can be thrown aside as useless, for they were based upon observations made by physicians of high intelligence and deep clinical insight.

Cullen attributed the disease to the direct influence of cold upon the joints which he believed to be vulnerable on account of their comparatively thin covering. Here he thought the inflammation commenced, and from them to generalise, and we have in this theory a recognition of the important factor of chill in the causation of the disease.

J. K. Mitchell suggested that the primary lesions would be localised in the spinal cord. Chill and exposure irritated the sensory nerve fibres over a wide area and set up this central disturbance which was in turn reflected to the nerves of the various organs and tissues and thus produced the manifestations. This view, based at first upon a study of cases of arthritis occurring in spinal diseases, was elaborated at a time

when the study of the nervous system was developing with great rapidity. It is easy to recognise in writings of that date (1831) that this system was taking too exclusive a position in the explanation of clinical facts, but the theory itself has greatly assisted in keeping before us the importance of the nervous system in rheumatic affections.

The *chemical theories* to which great impetus had been given by the classical investigations of the late Sir Alfred Garrod looked to uric acid or lactic acid as the exciting cause. In some respects the writings from this standpoint have seemed to us to have missed their mark because they tended to throw overmuch stress upon the constitutional peculiarities of the patient and to minimise the external factors that take so important a part in the causation of the disease. The lactic acid theory originated by Prout was supported by Fuller and Senator, and met with experimental support from the investigations of Sir W. B. Richardson, Rauch, and Sir Walter Foster. We cannot overlook the fact that Richardson and Rauch produced definite endocardial and pericardial lesions with lactic acid although other observers failed to confirm their results. Nevertheless, there has not been any conclusive demonstration of an excess of this acid in the tissues and excretions of acute rheumatism during the course of the disease.

Again Dr. P. W. Latham's and Dr. Haig's views that great importance should be attached to uric acid in the production of acute rheumatism, whether acting in conjunction with lactic acid or by itself, have not met with any convincing support from later investigators.

Theory of infection. Over a century ago Saunders suggested that rheumatism might be akin to malaria, and this was supported later by Maclagan, but modern investigations have shown conclusively that the two diseases are wide apart from one another.

The present position of the bacteriology is explained in the preceding papers, and here, without further discussion, the disease will be looked upon as the result of infection by a diplococcus belonging to the streptococcal group.

The diplococcus we believe to be present in all probability in the tonsils in the healthy subject, and it may possibly be present in many other situations. Under certain circumstances

and particularly in individuals whose parents have suffered from acute rheumatism this diplococcus develops pathological properties, gains access to the system, and sets up many and various manifestations. We do not suppose that the causation of acute rheumatism is to be summed up in the view that it is due entirely to the invasion of the diplococcus. Its presence in the tissues is no doubt essential, but there are important predisposing factors of much practical interest, and among these are the following.

1. *Heredity.* This is a striking feature which we interpret in this way. The rheumatic infection produces poisons of extreme subtlety, as is exemplified by the remarkable effect it may produce upon the nervous system of the young, altering, sometimes for years, the character and mental stability. Further, it is a disease which does not protect the patient from repeated attacks but on the contrary renders him more vulnerable. As a result a constitutional tendency—a tissue proclivity is developed which we believe to be transmitted in a greater or lesser degree to the children.

If we take the evidence obtained by the late Dr. W. B. Cheadle from his private case-books we find these figures. In thirty consecutive cases twenty-three gave a family history, and if we add to these the cases with chorea and erythema thirty-one out of thirty-three were found hereditary; combining arthritis, chorea and morbus cordis, 103 out of 180 gave a family history.

Hospital records, though less accurate are sufficiently convincing and carry the additional weight that they have been compiled by various independent writers who have each arrived at the same general conclusion.

Sometimes it happens that a mother in late pregnancy is the victim of an attack of acute rheumatism, and then we find that a different event may result. The infant may be born, not with a tendency to the disease, but with the active disease actually present. Morbus cordis may develop in utero, and in one case we demonstrated the diplococcus in vegetations on the mitral valve the second day after birth. Accordingly we hold that in exceptional cases there may be direct transmission of the diplococcic infection through the placental circulation.

2. *Sex incidence.* In childhood rheumatism occurs more frequently in females than in males, thus in 500 cases we found

319 females and 181 males. A very interesting point arises in connection with this sex incidence. The nervous system is much more frequently attacked in the female child, and chorea largely accounts for the predominance in the numbers. With chorea is associated mitral stenosis, and we find that this lesion which does not disappear as does the chorea in adult life is far more frequent in the female. To us it has appeared probable that some intrinsic peculiarities of the female metabolism may account for what we believe to be a broad general rule, viz. that rheumatism in this sex tends to be less acute but more obstinate. Doubtless it is a rule with many exceptions, but our experience has also led us to think that in the child, at least, rheumatism is more acutely fatal in the male, although as a result of chronic heart disease and the greater number of females attacked, the actual mortality among them is the higher. Thirty-six acutely fatal cases under our observation were made up of twenty-two males and fourteen females.

When adult life is reached it is clear that the male is more exposed to danger by nature of his employment, and in this sex the death rate, partly from the acute disease and partly from its previous injuries, rises in frequency.

3. *Age incidence.* The age incidence fully bears out the view that rheumatism is an infective disease. Almost any age is liable to an attack, and we meet with cases at two years or even younger, but it is not until after five years that the numbers begin to increase rapidly, and throughout childhood rheumatism is very frequent in this country. After puberty there is a decided fall in the frequency of nervous manifestations of the disease, and though it is common enough through adolescence and early adult life, the liability is less than in childhood and the manifestations less varied.

There are several interesting considerations that arise out of the question of age and its relation to rheumatism. Among these may be mentioned the possible influence of acquired habits in modifying the results of the rheumatic infection. Thus, for example, if we suppose an adult the victim of acute rheumatism in childhood to live a life such as we associate with the development of "goutiness," and then to be attacked by the rheumatic infection, it is an interesting speculation as to whether then he would not develop acute gout. This seems

to us a very possible occurrence, for it is quite conceivable that the inflammatory reaction to the infection might be intensely painful and that in the damaged tissues and exudations biurate of soda might be formed in the process of cell-necrosis.

Again, in the old or prematurely aged the rheumatic infection might well be associated with chronic changes of a stubborn character and degenerative lesions in the affected tissues, such as ulceration of cartilage and bone. We may seem to be drifting here into pure speculation but there can be no doubt that a disease of the inveterate character of rheumatism offers a valuable field for the study of the influence of changes in the human tissues resulting from age or acquired habits upon the behaviour of an infective process.

These preceding considerations which are concerned with the individual attacked by rheumatism raise the question as to whether there is a type that can be recognised as predisposed to the disease. This is the more interesting at the present time because the numerous modern instruments and methods of precision coupled with the increasing "specialism" of medicine tends to lead us into the danger of not realising the general and more indefinable effects of disease, and we are possibly inclined to believe that our accurate knowledge of disease in man is greater than it is in reality.

There has been handed down to us that in the adult the rheumatic subject has a coarse greasy skin and muddy complexion, but in the child this is certainly not the case. Such children are often fair-haired, with a bright alert manner, clear skin, but somewhat fragile appearance. They are excitable and easily tired, imaginative and subject to night terrors. More than others they appear to suffer from sore-throats and unhealthy tonsils. Digestive disturbances are frequent and take the form of attacks in which there may be vomiting with pale stools, or again, mucous colitis. It is difficult to decide how much in the constitutional weakness is the result of some actual invasion by the infection in a mild degree, but all who are well acquainted with these children realise that they frequently present similar characteristics.

One of the advances in our conception of rheumatism furnished by the view that it is an infection is the realisation that in addition to the peculiarities dependent upon the

individual we have also to remember that the infection itself possesses certain characteristics. These are difficult enough at present to express in clear terms, but they are widely recognised. A consideration of these brings us to the study of the influence of climate and season, locality, surroundings, atmospheric conditions, and other infections.

Climatic influences. Although rheumatism would appear to be ubiquitous, there is agreement that temperate climates in which there are considerable alterations in humidity favour the infection. In this country the disease is very frequent, and it appears to us that the lack of sun, cold winds and damp, must greatly favour inflammations of the throat. We have repeatedly noticed that when after a spell of dry heat with dust, cold rain and winds have followed, an outbreak of rheumatism occurs. The dust has favoured irritable affections of the throat and the cold and damp have precipitated the occurrence of chills and tonsillitis.

Seasonal influences. Intimately associated with the foregoing is the liability for rheumatism to increase when the late autumn and early spring seasons come round.

Epidemic influences. There would seem little doubt, for there are a considerable number of independent observations upon this point, that the frequency of the disease may increase so much in some years as to justify the term of epidemic being applied to the outbreak. This, however, would not seem to be a general but more or less local occurrence as is the case with polio-myelitis. We recall in recent years a remarkable frequency of the disease in North London, and letters from medical men apprised us of the same occurrence in country districts.

Such events as these will naturally raise in our minds the possibility that rheumatism may not only be infective but infectious. There is no doubt that several children may be attacked at the same time in one household, and we have met with instances of two children sleeping in the same bed developing the disease. Nevertheless, it would be wrong to promulgate the view that this is a frequent event or one that does not admit of other explanations. Tonsillitis is certainly apt to spread among the predisposed, and to this extent it is possible that members of a rheumatic family may be a danger to one another. Yet, on the other hand, to one of these

examples there are literally hundreds in which no such association can be recognised, and it must be admitted that in the exceptions there may be some other influence at work such as an unhealthy house or lack of care on the part of the parents for children who are predisposed by inheritance and in themselves delicate.

Influence of malsanitation. There is evidence that insanitary houses may be a cause of acute rheumatism which may assume a "septic" or "typhoidal" character. In such cases one individual may develop a "septic" pneumonia, another scarlet fever, a third acute rheumatism. There is no reason to look upon this occurrence as an evidence that rheumatism is an attenuated pyæmia, for the "septic" type may just as well be explained by the supposition that the malsanitation has either increased the special virulence of the diplococcus or lowered the resistance of the individual, or caused both these changes. We would particularly emphasise that we do not suppose that the diplococcus possesses some remarkable constant feature which results in its producing invariably the same results in the human body. We regard it as capable of altering considerably in virulence under different circumstances.

Influence of other infections. Diseases such as scarlet fever and measles, and we may add diphtheria, by causing sore throat favour, we believe, the danger of rheumatism, especially in the predisposed.

The *influence of locality* upon acute rheumatism is an exceedingly difficult study to which we believe fresh investigation might be directed in this country with useful results. Sir Arthur Newsholme many years ago pointed out that it was an urban disease associated with a low level of surface water. It is possible that the medical profession hardly yet recognises how frequent this disease is among the children in London. In our Children's Hospitals it is met with in all the medical wards and in numbers in the out-patient departments.

We have seen too many examples of cases arising in families who have changed residences and had the misfortune to drift into a damp house not to feel convinced that cold damp is most injurious, and one of the results that we have repeatedly noticed under these circumstances has been the persistent character of the rheumatic lesions. We believe that a rheu-

matic child living in a patently damp house and low-lying neighbourhood is very likely to develop a form of arthritis which is indistinguishable from so-called rheumatoid arthritis. It also appears to us that there is need for some further inquiry into the influence of residence upon rheumatism, for we have been struck with the fact that not uncommonly a child admitted into hospital makes a steady and good recovery, and yet repeatedly breaks down again on returning home, as if this return brought him into some peculiar surroundings which either roused up latent processes in his tissues or reinfected him. A clay soil is looked upon as the most unfavourable one for the rheumatic but it is clear that the drainage of any soil must also be taken into account. With houses, too, the question of damp cellars, thin walls, ill-fitting casements, and other weaknesses that result from cheap and bad work clearly require consideration.

Adults are less liable to develop rheumatism but the same general facts hold good as to damp, exposure, chills when heated, and malsanitation. Many, we must remember, under these circumstances do not develop the disease, but are already the victims of it from childhood.

Among surroundings not yet considered we must mention the elementary schools. It is very possible that where there are numerous colds and sore throats among the scholars the rheumatic child may suffer as a consequence. This is a difficulty which cannot be avoided where large numbers of children are collected together, but that it can be lessened by simple precautions is undoubted.

Dietetic influences. We have entirely abandoned the idea that diet has any influence in the incidence of acute rheumatism in childhood, for we can find no practical support for its truth and hold that it has been one of the mistaken results not uncommon in medical history of over-generalisation from some important clinical observation. The chemical theories centring round the discovery of uric acid and its antecedents are, we believe, the basis for this idea of the influence of diet. We look forward to the time when the theory that too much meat is responsible in any way for this disease in the young will disappear, however much imprudence in diet may modify its course in later life.

In general it may be confidently stated that those surroundings

which are associated with poverty and neglect are responsible for much of the acute rheumatism so rife in this country.

(*b*) The Pathology

i. *The Diplococcus Rheumaticus*

A brief account of the chief characteristics of the diplococcus will be given here in a summary.

It is a small micrococcus 0.5 μ in diameter and grows usually in pairs or in short chains. As a rule it does not show a capsule, but in the human tissues an appearance of capsulation may be occasionally noticed.

It stains readily with aniline dyes, but does not retain Gram's stain with great tenacity.

Degenerative forms are common, and the micrococcus then may become swollen or pear-shaped, and lose its staining properties.

Cultural characteristics. *In Bouillon* at 37° C. there is turbidity with a slight flocculent deposit in twenty-four hours. In three days the fluid becomes clear and there is a distinct deposit. The medium becomes acid.

On blood-agar—one of the most favourable media. In twenty-four hours, minute white colonies are visible : these tend to remain discrete and to alter the blood pigment to a rusty-brown colour. Upon this medium the micrococcus will live for long periods of time.

Milk and bouillon. Slightly acidified with lactic acid. This is a useful medium for isolation of the micrococcus. In twenty-four hours the milk is coagulated.

Vernon-Shaw used a medium of glycerine veal broth containing 2 per cent. peptone and 1 per cent. alkaline to phenolphthalein. Beattie directed attention to a very definite reaction in the production of acid and precipitation of the bile salts in McConkey's bile salt lactose broth.

Gelatine (stab). In forty-eight hours minute colonies appear along the track of the needle : there is no liquefaction.

The micrococcus possesses a considerable power of producing acid, and Triboulet and Coyon, Walker and Ryffel, Shaw and Berger investigated these acids and have shown that they vary with the medium in which the micro-organism is grown. Walker and Ryffel have particularly directed attention to the

large quantity of formic acid that the micro-organism forms and have extracted this acid from the bodies of the micrococci themselves. This micrococcus retains its vitality in the dry state for many months.

ii. *The Morbid Anatomy*

The experimental study of rheumatism coupled with the minute investigation of the tissues in man gives a most convincing proof of the nature of the disease. There are, in fact, few diseases the symptoms of which can be more satisfactorily explained if it be remembered that the exact nature of the poisons which are elaborated are as yet unknown.

The disease is the result of numerous separate lesions ; it is also one to which the human frame offers great resistance ; lastly, it varies as do other diseases in virulence. We see in the rheumatic process what we see in other infections, the tendency to widespread dissemination in the tissues of the young, and an increasing localisation in those of the adult. We find, too, the older tissues when they are attacked throwing off the effects of the disease with more difficulty.

In the subcutaneous nodule we discover the clue to the structure of the rheumatic lesions. In this there is a deposit of the infective agent and evidence of its results in the swollen connective tissue at the periphery, and the exudation and tissue necrosis in the centre. We also find the proof of tissue reaction in distended blood capillaries and leucocytic infiltration. Should the nodule be unusually large and chronic we recognise also the usual results of an imperfect victory in the presence of scar tissue.

Aschoff, Tawara and Carey Coombs have taken us a step further by the study of the still more minute submiliary nodules in which they find certain large multinucleated cells which they consider to be peculiar to the disease. Since the investigations of these writers we have studied these cells and have verified the truth of their descriptions, with the greater interest it may be added, because without appreciating their specific structure we had already depicted the submiliary nodule. To quote from Carey Coombs, "the submiliary nodules in myocardial rheumatism consist of rounded or fusiform areas formed by large spindle-shaped cells lying in the intermuscular trabeculæ of connective tissue." The

FIG. 106

Section of a sub-miliary nodule. We are indebted for this illustration to Mr. H. G. Butterfield. Following his description, *A* indicates the main giant-cell lesion ; *B*, smaller cells with single nuclei having precisely the same staining reactions as the giant-cell. This cell is in obvious association with the blood-vessel, the endothelial cells of which differ from it only in possessing single nuclei. Mr. Butterfield believes that the giant-cell is built up by the fusion of several endothelial cells of the same nature as those in the capillary wall, for under magnification, 1000, some of its components appear to possess a definite cell outline. This lesion was found in the epicardium of the left ventricle of a case of acute rheumatic carditis in which organisms corresponding to the diplococcus of Poynton and Paine were found everywhere in the heart. *Vide* "Heart," vol. iii, No. 2. Feb. 1912.

average size of them he would estimate as in length somewhat less than 400 μ. The special cells following the same writer are much larger than the fibroblasts of ordinary inflammatory reactions; to which in other respects they most closely approximate. They are often multinucleated, the chromatin substance of the nuclei in most cases appearing as a sharply defined margin with a small central mass or masses; the rest of the nucleus takes no stain and thus gives to the cell a vacuolated appearance. They are surrounded by plasma cells and leucocytes chiefly of the mononuclear variety. The nodules frequently arise in connection with an arteriole either around it or even in the wall itself, and their eventual fate appears to be cloudy swelling or cicatrisation.

Coombs, Miller and Kettle have recently advanced this subject a step further by demonstrating the submiliary nodules in the experimental lesions produced by the diplococcus; results which they published in the *Lancet* of November 2, 1912.

One warning we would, however, venture to give and that is against relying upon their presence as a criterion of acute rheumatism; and their absence as a criterion of the non-rheumatic nature of a lesion. This procedure would narrow the horizon of acute rheumatism down to a single element in morbid histology, and so far as our attitude is concerned, would destroy the broad basis of clinical, experimental, pathological and bacteriological observation upon which we have built up our view of the disease. Admitting then the value of these observations we would submit that these cells and nodules may only represent a particular phase of the rheumatic processes in the tissues and one which need not always be forthcoming.

When once the intimate structure of the subcutaneous and submiliary nodules have been mastered the elements of the morbid anatomy of acute rheumatism are understood. The pericardial, endocardial, myocardial, arthritic, pleural and meningeal lesions are all of the same nature when due allowances are made for the anatomy of the various structures and their particular resistance to the infection.

The Joints and Connective Tissues. In general terms and considering both the immature and mature tissues, the joints are the most vulnerable structures although their power of recuperation is far greater than that of a cardiac valve.

Arthritis. In acute rheumatic arthritis the synovial fluid is bloodstained, the synovial membrane swollen and extremely hyperæmic. Minute hæmorrhages occur in the synovial tissues, and the retiform tissue is infiltrated with leucocytes. In addition the connective tissue of the capsule of the affected joint is frequently swollen and infiltrated with serous exudation.

When the process is more prolonged the arthritic exudation becomes sero-fibrinous, and a plastic deposit may line the cavity.

There may be considerable implication of the surrounding tendons in the severe arthritis, and in some cases in childhood the tendons seem to suffer more than the joints themselves. The changes in these structures are of the same nature as those in the capsules of the joints.

As a rule the subsidence of the inflammation is rapid, and the recovery is usually complete.

We need only repeat here that cultures from the arthritis exudations are generally sterile, and in our opinion in the present state of our knowledge exploration for the purpose is seldom a wise procedure, for the micrococci are mostly destroyed in the tissues and in the cells of the arthritic exudation.

We come now to a problem which is deserving of the greatest attention. It is repeatedly stated that the arthritis of acute rheumatism subsides rapidly and completely, and that it is very unusual for any local injury to persist after the attack. With this we are in general agreement although we have met with very definite examples of one joint, among many which subsided, remaining painful and swollen and passing into a condition of " rheumatoid arthritis." It is to be expected that the acute form of rheumatic arthritis would as a rule subside, for it is a synovitis and the affection rapidly destroyed, but there are other forms of rheumatic arthritis, we believe, both in the young and the adult. Cases which begin, as do other rheumatic lesions, gradually, and with warnings which are possibly overlooked and which run a tedious and sometimes crippling course. Every variety is found. Sometimes in a child there is distension of the cavity of a joint with fluid from which the diplococcus may be isolated and from which there may be excellent but slow recovery ; or again, at an early age the course may be extremely chronic. In young adults the

process may be not only prolonged but malignant in type, and great damage result. Associated with mitral stenosis there may be an equally slow damage to the joints, and in the adult a chronic arthritis with deformities may follow. That all cases of subacute and chronic non-suppurative arthritis are not rheumatic is undoubted, but to maintain that the rheumatic infection does not produce every kind of arthritic injury appears to us to be mistaken. The great difficulty at the present time is to demonstrate the cause in the particular case, but we hold that this infection may damage synovial membrane, capsule, cartilage and bone. It may attack small as well as large joints, and may even in the young sometimes produce a very chronic spondylitis deformans ; or in a great toe joint an acute inflammation almost indistinguishable from a gouty arthritis.

A study of the connective tissues of the synovial membranes both in man and in experimental arthritis gives a very clear idea of the cardinal processes that occur.

When acute there are active hyperæmia and swelling of tissue, exudation, leucocytosis and necrosis, when chronic, perivascular fibrosis occurs with the usual diminution of the calibre of the small blood-vessels and consequent imperfect nutrition of the synovial structures. The tendon sheaths as well as the tendons themselves often suffer and an exudation results which in the worst cases is followed by painful adhesions. Local periostitis around the affected joints is met with both in childhood and later life, and in the young is often associated with the development of subcutaneous nodules. Such periostitis may also occur at a distance from an affected joint.

The subcutaneous nodules having already been described, it remains here to comment upon their peculiar distribution, along tendon sheaths and over bony prominences. In the paper written with Dr. Still it was shown that the same process might be occurring in the connective tissue *without producing visible swelling*, and it would seem to us that the visibility of the nodule is largely dependent upon the fact that the least swelling is thrown into relief when it occurs over a bony prominence, and thus our attention is arrested. Yet there is probably also another factor, and this is the amount of movement, pressure and friction to which the tissues over these bony prominences are exposed, in other words there is an

element of injury concerned which increases the severity of the local infection in these positions.

The distribution along tendon sheaths, though probably influenced by the movements of the tendons, is also, we think, dependent upon the synovial sheath being in nature akin to the pericardium, and that the process in this structure is particularly active. These nodules along the tendon sheaths which occur with so little disturbance are most interesting when the reader studies them in connection with the pathology of chorea. Nodules vary very much in duration from a few days to many months. Usually they disappear entirely, but if they are large some thickening will remain.

Doubtless the *fasciæ* suffer much in rheumatism, and with the fasciæ the *muscles* and *nerves* also. The term fibrositis coined by Sir William Gowers is a useful one in this relation, but it is one which is very open to abuse. Pathologists recognise that any infection travelling in the blood stream gets a foothold in the tissues by escaping from the minute capillaries running in the connective tissues binding together the various organs. If fibrositis is used then to denote a specific disease it can only result in confusion, for if ever there was a condition that was truly a symptom, it is this one. Rheumatic fibrositis is frequent and occurs at all ages, for even in young children we meet with stiffness of the muscles, lumbago and intercostal pains. In adults these symptoms are far more frequent and more chronic. The actual proof of the cause of any particular fibrositis is extremely difficult but the clinical evidence in favour of a rheumatic form is overwhelming. In severe cases we can detect deep-seated tender nodules in the muscles arising in their fasciæ. The work of Froriep long ago directed our attention to these changes, and Professor Stockman in this country has done much to impress their importance upon us in recent years.

To summarise at this point the results that we should be prepared to meet with from our investigations upon the pathology of arthritis and fascial lesions: These would be localised deposits of the diplococcus, swelling and infiltration of connective tissue, necrosis and exudation, capillary hæmorrhages with the formation of nodules varying in size from the submiliary to those easily palpable to the fingers when lying deep, or as large as a filbert when subcutaneous. Theoretically

no fasciæ would be exempt although there is no doubt that some regions are more affected than others. When the muscles grow older with advancing years it is easily realised how these changes may produce great pain and crippling, for if fibrosis occurs and sensory nerves are implicated the harmonious and painless contractions of the muscular fibres will be interfered with, and in the early stage of infiltration and connective-tissue swelling the same must occur and be probably more widespread and accompanied by a distressing sense of muscular weakness.

A very interesting subject for study is the individual differences in reaction to the rheumatic infections in these tissues. In some instances we find a remarkably widespread puffiness of the affected regions, giving rise in the hands to much swelling and difficulty in closing the fingers. In other cases there are numerous subcutaneous nodules which give rise to little or no pain ; in others the periosteal inflammation is considerable and the bones around the joint may be in the adult very tender. The extent to which these differences are dependent upon the infection or upon the individual is a difficult question for solution.

Under the section of Ætiology we have expressed our conviction that acute rheumatism is a disease that is not dependent upon dietetic influences ; we do not, however, deny that in the adult and elderly persistent errors in diet will produce injurious effects upon all tissues and thus tend to modify the results of the rheumatic infection. Simple wear and tear of the tissues we should suppose would have also an important effect in the same direction.

Pathological changes in the heart and pericardium. Simple pericarditis. As a result of deposition of the diplococci, hyperæmia and capillary hæmorrhages result with swelling of the connective tissue and coagulation necrosis of the tissue cells, exudation of serum and diapedesis of leucocytes from the blood capillaries.

The endothelium lining the pericardial sac is destroyed in many areas and there is an exudation into the cavity varying in character according to the duration and virulence of the process. Thus it may be bloodstained, serous, sero-fibrinous, or sero-purulent.

The amount of effusion is usually moderate, but there may

be much fibrino-plastic exudation on the visceral and parietal surfaces of the pericardium, and in exceptional cases a large effusion.

In malignant cases of rheumatic pericarditis there is great thickening of the pericardium and the inflammation may spread into the adjoining mediastinal tissues. Nodular masses of necrosis may occur in the parietal layer, and large deposits of bloodstained fibrino-plastic exudation are found.

In a third form the process is slower and less virulent and results in a gradual fibrosis of the pericardial tissues with complete adhesion of the pericardium. Should other serous membranes such as the pleuræ and peritoneum be then attacked by the rheumatic infection the syndrome known as multiple serositis may develop. This condition, however, would seem to be rare in rheumatism and to be much more characteristic of tuberculous pericarditis in which the much thickened pericardium strangles the heart and thus produces one of the great factors in the development of the illness.

It is from the pericardial exudations that the diplococcus is most easily obtained, doubtless because this lesion is as a rule the result of a severe attack.

Endocarditis. The bacteria are carried in the coronary circulation to the neighbourhood of the valves and as in pericarditis produce various results. We find them in the subendothelial tissue causing cell proliferation and necrosis with the formation of minute projections from the margins of the cusps which become later the vegetations. These are firmly attached to the substance of the valve, gradually merging into the normal structure. Fibrin may or may not be deposited upon these vegetations which when they heal do so by the usual process of fibrous tissue formation. In acute rheumatism active endocarditis of the *simple* type is not fatal, and the diplococci are, as we should expect, not as a rule found in large numbers in the cardiac valves but are rapidly destroyed just as they are in the walls of the vermiform appendix. When acute rheumatism proves fatal from carditis the valvular lesions are usually quieting down, and they are difficult structures to take cultures from without contamination, even by the method of reinforcement. Various investigators have, however, confirmed our demonstration of them in these tissues, and have isolated them from the vegetations.

When the rheumatic process is *malignant* the vegetations contain great numbers of the diplococci, and the areas of necrosis are much more extensive. The obvious lesions may then spread some distance from the cardiac valves and may in the case of the aortic and mitral valves spread from the one to the other by direct extension. It should, however, be remembered that experiment has shown that in the "simple" type of infection, the diplococci are to be found under the endothelium lining the cardiac cavities in the neighbourhood of the valves, but they produce such minute lesions as to be invisible except under the microscope.

Between the frankly "malignant" and the "simple" forms there are to be found all grades of severity and there are left in many vegetations of the "simple" type, areas of necrotic tissue which we look upon as elements of danger for the future. The duration of the activity of endocardial vegetations is a subject which still requires further investigation.

We attach much importance in the history of rheumatic heart disease to the presence of these foci of necrosis which have not completely healed, because we look upon them as areas of danger in which the diplococci probably live for weeks, months or years.

There is a third process in the history of rheumatic endocarditis which must be mentioned and that is a slow persistent one producing gradual fibrosis of the valve segments, chordæ tendineæ, papillary muscles, and valve ring. This is best exemplified by the well-known mitral stenosis, but the same order of change may be met with in the tricuspid valve and sometimes in the aortic producing stenosis of the valvular apertures.

This insidious inflammation may follow upon an acute attack, but may also develop from the first and year after year may remorselessly advance, doing irretrievable damage, with symptoms of the very slightest to give us warning of the true state of affairs.

The myocardial lesions in rheumatic carditis are twofold. The interstitial which have been already described in the earlier part of the article under the submiliary nodules, but which may also in our experience be sometimes considerably more than submiliary in size and the lesions of the muscle

fibres themselves, which are also focal and of which the most definite are the fatty changes.

The extent of these lesions varies in different cases and we must beware of over-rating their gravity, for there are many cases of fatal rheumatic morbus cordis in which they are of only slight degree.

It is in the virulent cases with much dilatation that they are the most definite, but further experience both of the morbid anatomy and clinical history of rheumatic carditis is needed to establish on sure ground our accurate knowledge of these lesions.

It is in this direction that we await further light from a study of arrhythmias in active rheumatism by the recent methods of electro-cardiography.

In any consideration of the myocardium we must not lose sight of the implication of the cardiac nerves in the focal lesions and of damage to the auriculo-ventricular bundle and its ramifications.

Extensive fibrosis of the myocardium would seem to us to be an exceptional event in rheumatic heart disease, but again upon this point there is need for more inquiry.

The rheumatic infection, although it may produce an *arteritis* does not appear to damage the arteries to any great extent in the young, and in older subjects it is difficult to decide when there is extensive arterial change, what part, if any, the actual rheumatism has taken.

Embolism is an important cause of arterial damage, and when malignant in type the larger arteries may as a result give way from secondary disease in their walls, or again aneurysms result.

It is quite possible, though incapable of proof, that some mild degree of infection of the vessels may occur without being of any clinical importance, but among results possibly a tendency to spasm should be added.

The perivascular fibrosis that occurs in the numerous lesions of rheumatism may possibly, when extensive, produce some injurious results upon the circulation by curtailing the vascular supply and raising the blood pressure, but it is a result that it is difficult to appreciate.

Phlebitis, as one of our earlier papers illustrates, may, in exceptional cases, be severe and dangerous to life, but in this country it is not recognised as a frequent occurrence.

It would be wearisome to repeat in detail the morbid changes that occur in every organ that has been attacked by the rheumatic infection, but a few words may be devoted to such important ones as are associated with the nervous system, the respiratory tract and the kidneys.

The Nervous System. We recognise in the nervous system as we do in the heart two orders of lesion, those of the connective tissue and of the nervous tissue proper ; but the general result that appeals to us is that the rheumatic poisons are not very actively destructive to the nervous tissues although highly irritant.

Diplococci are deposited in the pia mater in the neighbourhood of the minute blood-vessels and set up the usual changes, among them the formation of submiliary nodules as recorded by Fraenzel. In the brain the diplococci are also found close to the minute blood-vessels in the connective tissue supporting them, and more rarely in masses in the neuroglial tissue.

Thrombosis, perivascular exudation and small areas of softening occur as a result of the infection, and in the nerve cells throughout the brain there result the evidences of a toxic process in the alterations in the nuclei and tigroid, and the definite but slight damage to the medullated nerve fibres.

The meningeal changes recall in their behaviour the subcutaneous nodule, although we are inclined to the view that in rare cases an acute meningitis may result as recorded in one of our papers.

It seems also possible that in the exceptional condition of *rheumatic hyperpyrexia*, there is an unusually virulent cerebral toxæmia rather than an overwhelming invasion of the cerebral tissues by the diplococci. Upon this point our evidence is at present, however, very scanty.

Interstitial and parenchymatous changes must in all probability occur in all parts of the nervous system and may well explain the neuritic pains and more definite symptoms recognised as rheumatic sciatica, and cervico-brachial neuritis.

There is doubtless more to be learnt in the future as to the possibility of perivascular fibrosis in connection with the nervous system producing chronic spinal conditions such as disseminated sclerosis, and as to whether or not a virulent rheumatism may not also in exceptional cases damage acutely

the nerve tissue itself. A certain amount of clinical evidence in favour of such possibilities is on record.

The Respiratory System. The Tonsils have attracted great attention and with good reason, for there can be no doubt that unhealthy conditions of the tonsils and naso-pharynx are, especially in childhood, closely associated with acute rheumatism.

The direct sequence of a sore throat and acute rheumatism is too frequent an event for us to escape from the conviction that they are directly associated.

The balance of evidence at the present time favours the view that in angina faucium of rheumatic nature there is a rapid multiplication of the strepto-diplococci. The pathological changes in the tonsils vary with the virulence and chronicity of the processes. Thus acute general inflammation, foci of inflammation with follicular exudation or a fibrino-plastic exudation may be met with. If the attacks are repeated enlargement of the tonsils results and in their depths there may be foci of disease with areas of necrosis which are hidden from view. We have found such areas bound down under the scar tissue of an amputated tonsil. Some enlargement with tenderness of the cervical lymphatic glands is frequent, and is strictly analogous to the enlarged mediastinal glands that are found associated with severe rheumatic pericarditis. Rheumatic infections of the nasal passages and naso-pharynx require further investigation.

The bacteriological investigations connected with these tonsillar and nasal lesions are necessarily difficult on account of the various bacteria that are to be found in these structures, and this difficulty has undoubtedly delayed the progress of investigation.

Rheumatic affections of the articulations of the larynx seem to be very unusual, at least in childhood, and laryngitis does not appear to be a part of an acute rheumatism.

Pleurisy is, however, frequent, and is almost always present in the worst cases of rheumatic carditis in childhood. Usually it is a "dry" form, but there may be sufficient effusion to demand tapping, and then a sero-fibrinous exudation is withdrawn, from which the diplococcus has been isolated in pure culture.

The question of an isolated infection of the pleura is a very

difficult one to express an opinion upon. *Bronchitis* has been thought by some to be a symptom, but we have no facts bearing upon this point.

In the lungs, apart from infarction, we recognise two conditions, a broncho-pneumonia and an acute œdema.

The broncho-pneumonia is associated with the presence of numerous diplococci in the alveoli. These must, it is clear, be distinguished from the diplococcus lanceolatus. The exudation is sero-fibrinous and there is often a good deal of pulmonary collapse around the pneumonic areas. In virulent cases there are sub-pleural ecchymoses and also hæmorrhages into the alveoli.

Pulmonary œdema occurs as an exceptional event in the course of an acute rheumatic carditis. It is a very definite if rare lesion, the lungs rapidly becoming œdematous from above downwards. Whether the condition is directly rheumatic or the result of a failing circulation or of depressing remedies has not been decided, but it may occur without any evidence of severe renal disease. Sections show the alveoli full of a serous exudation.

In the kidneys the changes produced by the rheumatic infection are less clearly understood. They would, however, appear to be of much the same character as in other organs : thus acute nephritis may result or a toxic action on the essential cells may cause their necrosis. Infarctions may produce localised areas of sclerosis, and judging from a study of fatal cases of mitral stenosis, a general renal sclerosis may also occur. This has been also described by Drs. Cowan and Fleming, who consider it to be the result of various causes. In 1905, in Osler's and Macrae's system, we gave some clinical and experimental facts which support the view that the stenosis of the mitral valve and sclerosis of the kidneys may be both of rheumatic origin. The diplococcus can be isolated from the urine in virulent cases of acute rheumatism.

The pathology of the *alimentary canal* in rheumatism is a subject but little understood and yet of great interest. All medical men are acquainted with the view that rheumatism may be the result of auto-intoxication from the bowel, and many believe that there may be a direct infection from the bowel, as there may be from the tonsils.

At present the facts ascertained about appendicitis are perhaps the most accurate at our command.

We know that the diplococcus isolated during life from a case of acute rheumatism may, on intravenous inoculation, produce appendicitis of varying severity in young rabbits. We also know that a diplococcus obtained from a follicular tonsillitis in a child has been isolated from an appendix which was also simultaneously in a state of inflammation, and that the diplococcus produced appendicitis, arthritis and endocarditis in young rabbits.

Our later investigations have shown the close pathological resemblance between the changes in the animal and human appendices, and led us to recognise dilatation of blood-vessels, necrosis of tissue, fibrino-cellular exudation and leucocytosis, together with destruction of the diplococci by the living tissues. The chronic changes in some cases of recurrent appendicitis in man are comparable to those in chronic rheumatic arthritis, myocarditis, pericarditis or endocarditis.

These pathological results have this particular interest, that they show that an intravenous inoculation may produce an appendicitis and an arthritis, or an arthritis alone. They also illustrate that in animals the association of an arthritis with an intestinal lesion, does not by any means prove that the arthritis is a result either of auto-intoxication from the intestine or even auto-infection by that route. Evidence of this nature, although only based upon animal experiment is a useful warning to us to accept with caution dogmatic assertions that rheumatism is the result of an auto-intoxication from the bowel, and to keep before our mind the other possibility that alimentary disease and arthritis, when co-existent, may both depend upon a common cause arising in some focus distant from either.

The pathology of the alimentary system in acute rheumatism is so little known because there is little clinical evidence at present pointing to severe abdominal affections resulting from the disease. Appendicitis is still *sub judice;* mucous colitis in rheumatism is not fatal and the other abdominal symptoms are also transitory, although gastric symptoms in the adult associated with dilatation may be severe.

In concluding this section we must allude to the question of *dental caries and gingivitis.* The work of Mr. Goadby upon pyorrhœa and alveolarum in this country is well known, and to us there seems to be a wide field for investigation in this

direction. Writing with the greatest caution and trusting solely to clinical experience, we are not as yet convinced that dental disease is closely associated with acute rheumatism in childhood. Because an arthritis may arise by an infection from diseased gums this does not necessarily imply that acute rheumatic arthritis has such an origin. Further study of the question is required, and in the future no doubt more evidence for or against rheumatic infection through the gums will be forthcoming.

This general outline of the pathology of acute rheumatism prepares us for the acceptance of the fact that the symptoms are numerous and vary greatly with the virulence of the infection and the extent of the tissues involved.

SYMPTOMATOLOGY

We are able to explain the clinical symptoms of acute rheumatism by the view that we have put forward with considerable accuracy, and, we think, much more clearly than is possible by any other explanation of its causation.

Two general statements can be made upon this subject of the symptomatology. The first, that in the future all descriptions of acute rheumatism will be probably based upon a survey of the disease in the young, and such peculiarities as occur in adult life will be looked upon as departures from the classical disease which is seen in its truest characters in childhood. The second, that the symptoms do not always combine to produce an acute disease running a definite course. On the contrary the symptoms may not only be at first indeterminate, but they may even occur as isolated events pointing to the implication of one important organ only. Thus there may be a characteristic rheumatic fever or an illness with numerous equivocal symptoms which at last develop and betray the real condition, or there may be a solitary carditis, polyarthritis or chorea. Any description of the symptoms of acute rheumatism must then be almost as formidable an undertaking as a description of tuberculosis.

For the present the most satisfactory plan would appear to us to give first an outline of the acute general disease as it occurs in the young and the adult, and then to give the symptoms of the chief local manifestations as they occur under different conditions of virulence and duration.

Generalised Rheumatism. An acute severe attack in a *child* runs somewhat this course. After a more or less definite history of a chill or exposure, a sore throat develops which may

be red and relaxed, or may be a follicular tonsillitis or more rarely a tonsillitis with a fibrino-cellular membranous deposit upon the surface. There are malaise with fever, pains in the joints and muscles, and prostration. If the virulence is high vomiting and diarrhœa may usher in the illness. Several articulations become swollen and the skin over them may show a red flush. The knees and ankles among the larger joints are very frequently attacked ; but the smaller joints may suffer also. Pain in the chest directs attention to the heart, which is found to be acting rapidly and to be dilated, and later endocarditis and pericarditis appear. An erythematous rash may be noticed, or after some headache choreic movements develop and later again subcutaneous nodules. Anæmia soon becomes apparent, and within three weeks it is clear that the child is the victim of a severe attack of rheumatic fever.

In the *adult* the acute disease described so definitely in all our text-books, does not appear to us to be so frequent an occurrence in our hospital wards as it did twenty years ago. When a classical example occurs, there are usually the same chilly feelings and sore throat with malaise, prostration and fever. There are the muscular pains also, but the thickly coated tongue, profuse sour-smelling sweats, rapid and severe polyarthritis make a clinical picture so striking that it has been thought by some that the disease is not identical with the acute rheumatism of childhood. Cardiac affections of severity are not so frequent, but dilatation and valvular disease are common enough in the adult.

These acute cases in the adult are usually first attacks. When, however, we follow the history of rheumatic children through adolescence into adult life, it becomes apparent that the later attacks, though often not so severe as in childhood, resemble them very closely, and that there are a great number of examples of acute and subacute rheumatism which are obviously of precisely the same nature as those that occur in childhood.

The peculiarities that we notice in following these histories are : the decreasing tendency to develop nervous manifestations, and a general diminution in the variety of symptoms ; an increasing tendency for the disease to linger in the organs that are attacked and sometimes with this chronicity the

development in the heart of malignant forms of endocarditis and in the joints of damaging arthritis.

The peculiar smouldering type of the rheumatic process which in childhood shows itself in repeated chorea and in the early stages of mitral stenosis becomes very apparent in the adult female in the severe mitral stenosis so repeatedly associated with repeated attacks of mild arthritis and muscular rheumatism.

We venture to think that the influence that alterations in the tissues from age and habits must exert upon the behaviour of the rheumatic infection has not yet had a fair field for observation, and in great part for two reasons ; the routine description of rheumatic fever or acute rheumatism as an acute process, and the barrier raised to a broad study of the disease by those who maintain that salicylate of soda is to be the criterion of a rheumatic lesion.

The exacerbations of the disease in childhood may show themselves in the development of different manifestations. An illness commencing with polyarthritis and carditis may quiet down and then chorea develop, or nodules commence to appear. In the adult arthritis is the most constant symptom, and exacerbations of arthritis are the most frequent events in the relapses.

Course of acute rheumatism. If we were asked to give an account of the course of tuberculosis we are convinced that no one would expect to obtain an adequate answer. The same is equally true of rheumatism. There is no one who can confidently describe the course of rheumatism, or who knows when the disease is cured or only latent. Clinical experience of tuberculosis enables us to predict with a certain amount of accuracy the course of the acute generalised disease, or on broad lines that of the pulmonary, abdominal or meningeal form.

So too, with rheumatism, we know with some degree of certainty the course of some of the chief types we may choose as illustrations.

Virulent generalised rheumatism may prove fatal in the first attack or be imperfectly recovered from after many months. Acute rheumatic fever in the adult may be completely recovered from after many weeks or leave some permanent injury to the heart.

Mild attacks in the child and adult may quiet down in three

weeks. The course of rheumatic arthritis is usually favourable, of rheumatic heart disease only partially so. Malignant local lesions are either dangerous to life or only damaging in accord with the particular organ thus attacked. The nervous phenomena in rheumatism are as a rule transitory. Thus we find ourselves repeating much the same experiences, differing, of course, in detail, as those that are met with in tuberculosis, in which, too, we are also confronted with the difficulty of deciding whether the disease is cured or only latent.

The Symptoms of the Local Manifestations

Arthritic, muscular and fascial inflammations. The pain and swelling need but little comment ; they are less severe in childhood and the pain is frequently in the region of the tendons, and often is more severe when there is little or no swelling of the joints themselves. When there is considerable periarticular swelling, whatever the age, it is an indication that the infection is obstinate in type and will be slow in subsiding, for it points to very definite infiltration of the capsules of the joints with the inflammatory exudation. Even in the young if this subacute process persists there may be some damage to the cartilages.

Although a monarthritis is exceptional it may occur at any age, and when it affects the right hip joint may, in childhood, be mistaken for appendicitis. In the young also the small joints of the fingers and toes may be prominently affected, and spindle-shaped swellings result in consequence. Muscular wasting may also be very definite if the arthritis is unusually severe and prolonged in duration.

Bursæ may be implicated and ganglionic swellings appear in connection with the sheaths of the tendons.

Again in the young obstinate cervical arthritis may occur, simulating very closely spinal caries and in rare cases resulting in spondylitis.

Realising these varieties in the arthritis in the young at an age when these structures are untried by constant wear we cannot but believe that in the elderly adult acute rheumatism may produce all forms of arthritic damage.

Fibrositis is much less frequent in the young, but it is well recognised as a lumbago, or even a general stiffness such as we associate with the elderly. These lesions are sometimes

very puzzling when strictly localised, persistent pain in the heels may suggest, for example, tuberculosis of the os calcis, and stiff neck caries of the spine. It is probable that some of the obscure abdominal pains in rheumatic children are also the result of a fibrositis in the lower intercostal or abdominal muscles. A mild periostitis around the inflamed joints, particularly the knee-joints, is met with in some cases, often in association with subcutaneous nodules, and it may also occur in the form of a local node at a distance from a joint.

The *subcutaneous nodules* are now thoroughly recognised and have been found in young adults as well as in children, although they are unusual after puberty. Their situation over bony prominences and along tendon sheaths needs no further comment. They are curiously painless and vary very much in size and duration. Although a rule with exceptions, their occurrence is usually associated with heart disease. Sometimes when all other symptoms appear to be in abeyance these nodules commence to appear in various situations, and such an event always indicates the danger of some more serious manifestation arising. When chorea develops during this phase it is tempting to believe that similar painless nodules are developing in the meninges.

Purpura may occur round a nodule and in rare instances become a little tender. The nodule attaches itself to the skin, but never seems to produce more than a slight dull redness. The rule, however, is for the skin to move freely over them and to remain natural in colour.

In malignant endocarditis we have seen large nodules and have demonstrated the diplococci in their dilated blood-vessels, but such nodules are, we believe, rare.

These lesions must be distinguished from the minute tender swellings which are frequently noticed in chronic cases of malignant endocarditis at the finger ends and sometimes elsewhere (Osler's sign). These are of the nature of minute *emboli*, in terminal blood-vessels.

The cardio-vascular manifestations. These are cardiac dilatation, endocarditis and pericarditis, the most characteristic clinical conditions being a general carditis.

The symptoms of the *early acute cardiac dilatation* namely: a quickened low pressure pulse; a feeble impulse displaced outwards; an enlarged deep cardiac dullness; and a short

first sound at the apex with or without a soft systolic bruit, coupled with an accentuated pulmonary second sound at the base, deserve the closest attention. They are the first danger sign, and although unfortunately mitral endocarditis is frequently associated, it is certain that this dilatation may appear and subside leaving no damage behind.

Acute pericarditis. This is the lesion of the heart which, particularly in the adult, is most often associated with obvious signs of cardiac injury. Precordial pain, breathlessness, pallor, vomiting, fever and delirium may all occur. Yet in the child the symptoms may be few. Pericardial friction and a diffuse and excited impulse are very frequent signs, but it is exceptional for the effusion to be so great as to demand paracentesis, and in our experience such an event is very rare. This lesion points to a grave infection and it is by far the most frequent cause of death. Nevertheless pericarditis usually proves fatal by supervening in a case in which the heart has already been damaged, and though a first attack may prove fatal it is unusual. We must remember that a pericarditis may be chiefly limited to the back of the heart and is then very difficult to detect. Endocarditis is almost always, but not invariably associated.

Acute endocarditis of the simple type gives rise at first to very few symptoms, although some rise of temperature is frequent. The mitral valve is the most frequently attacked and next the mitral and aortic valves. This latter lesion has not attracted sufficient attention in the young. It is not only a frequent occurrence, but a very serious one. Both valves may be attacked in the same illness, but more often the aortic is involved the later, and should this lesion then predominate the outlook is not good. A pure aortic regurgitation is rare in childhood but may occur as it does also in experimental heart disease.

The study of the morbid changes prepares us then, to realise that the heart disease of rheumatism may become established in the young with very little, if any, clinical evidence of its occurrence. We have only to picture the minute lesions of a mitral endocarditis to see how probable this must be. When the injury is a chronic one of the nature of a mitral stenosis and the only organ attacked the heart, can there be any wonder that we are repeatedly meeting with cardiac lesions of

mysterious origin? Experience indeed teaches us that we often rely for the detection of rheumatic heart disease upon the warnings given us by such other manifestations as arthritis and chorea. We do not mean to imply that with a severe carditis there are not very definite indications in precordial pain, breathlessness, pallor or cyanosis, and general wasting, but we are anxious to direct attention to the great difficulty we have in approaching the problem of the prevention of rheumatic heart disease on account of the few clinical signs that may present themselves. In the adult the myocardial damage produces symptoms much more constantly and rapidly, and the severe results of an acute pericarditis are thoroughly recognised.

We would repeat that the insidious way in which at an early age the mitral and aortic valves may both be damaged is a clinical fact which should always be before our minds.

The *myocardial damage* is of great practical importance, and for the last ten years we have repeatedly directed attention to a particular group of rheumatic cases in childhood, in which, together with breathlessness and general nervousness, the heart remains dilated and the pulse excitable and irregular, but there is no sign of a valvular lesion or at the most a soft systolic murmur audible at and internal to the left nipple.

Such cases are obstinate and easily break down under strain. In adults the same condition is met with, and rheumatism is one of the causes of those dilated irregular hearts which are so adversely influenced by alcoholism or undue physical or mental strain.

Death from acute dilatation of rheumatic origin is very rare, but such cases investigated by Dr. S. West and Sir James Goodhart, gave us in this country some of the first important facts upon myocardial disease in rheumatism.

The chronic forms of progressive rheumatic heart disease are represented by mitral stenosis, and the rarer aortic and tricuspid stenosis by chronic myocarditis and chronic relapsing pericarditis. The severe types of infection are recognised in the virulent carditis of childhood. The healed lesions of the heart are represented by chronic heart disease and adherent pericardium.

One condition stands out as a special one by reason of the peculiar relation of the lesions to the general blood stream,

this is the *subacute malignant form of rheumatic endocarditis.* The morbid anatomy shows us necrotic tissue and blood clot full of the diplococci, projecting into the blood current within the heart, and clinical observation provides the symptoms that must result from the general dissemination of the infective agent either alone or with loosened clot or necrotic vegetation. There result : general constitutional disturbances more or less paroxysmal, in accordance with the liberation of the infection into the general circulation and evidenced by fever, sweatings, and possibly rigors and diarrhœa : local lesions the result of emboli, which, if minute, produce purpura or nodosites cutanées ephémères (Osler's sign), and if larger, emboli in various organs or vessels.

In addition to these cases others are met with, which, after showing some of the signs of malignant endocarditis over periods of several months, eventually quiet down leaving the heart grievously damaged.

Arteritis is extremely rare as a clinical feature in acute rheumatism, the occasional changes that are found in the first part of the aorta giving rise to no symptoms during life. On the other hand we have seen from time to time arterial spasm with the phenomena of Raynaud's disease, including local gangrene, follow upon an acute carditis, the first signs showing themselves within six months of the cardiac attack.

Phlebitis. The nature of the symptoms are well illustrated in our paper (No. VI) upon this subject, in the first part of this book.

The nervous manifestations of rheumatism are among the most interesting of all the phenomena. Chorea stands out as the landmark, but the pathology of the disease prepares us to expect that there may be often enough signs of disturbance which stop short of a declared chorea, or may antedate it for some weeks.

Of these signs those of cerebral irritability and headache with mental and psychical instability are the chief. The choreiform movements may be slight or extremely severe, acute or gradual in onset, and transitory or very prolonged in duration. The pathological evidence that many of the nerve cells are affected by the poisons, is amply borne out in the clinical study of chorea. The extent of disturbed movement including, as Dr. Langmead has shown, nystagmus, and the

psychical and intellectual disorder are sufficient proofs of this statement. The paralytic type may almost merge into a definite embolic hemiplegia, and suggests in some cases an abrupt focal invasion of the tissues by a considerable number of diplococci. Of great interest is the fact that though the cerebral tissues do not seem to suffer very severely in the rheumatic injuries they show great difficulty in throwing off the effects. We see also very clearly the influence of predisposing factors in the powerful effects of fright, and cerebral strain in predisposing to the onset of chorea, and again we recognise that this form of rheumatism is very closely associated with the insidious lesion of mitral stenosis and shares with it its tendency to attack females.

The rheumatic origin of chorea receives interesting support from our recent figures.

In 217 cases, 122 gave evidence of heart disease and other rheumatic manifestations. In twenty-eight more there were arthritic and muscular pains; in twenty-two more cardiac dilatation. Ten more followed a sore throat. Twenty of the remainder gave no history of any cause, but two of them later developed acute rheumatism. Fifteen were attributed to fright and shock, but in some of these no direct relation could be traced, and they were certainly rheumatic in later life. Eight were directly attributed to strain at school.

The remarkable decrease of chorea after puberty suggests that in the adult a search for rheumatic cerebral symptoms may in the future discover that the disease still retains more influence upon the nervous system than we perhaps recognise.

Rheumatic hyperpyrexia needs no description here for it is recorded with detail in all the leading text-books. The condition points to a virulent process, but the actual facts at our disposal are so scanty as to make it unwise as yet to offer any further suggestion than that it represents some peculiar virulence rather than an overwhelming degree of infection with the diplococci. The signs of meningitis and of the rare spinal lesions are in no way peculiar.

Rheumatic neuritis is a very painful, and for this reason important, result of rheumatism, and one much more prominent in the adult. The symptoms depend upon the particular nerves affected, but in all cases pain is the striking event.

Respiratory system. Passing mention must be made of *epistaxis* which, as Dr. S. Phillips has pointed out, is not infrequent in rheumatic children, and may be among the first warnings of an attack. It is sometimes profuse, but repeated attacks rather than a single severe one are more usual. It may be associated with a tendency to develop bruises on slight injury and other signs of a hæmorrhagic tendency.

The importance of tonsillitis has been insisted upon, and to this we must add the danger of chronic unhealthy large tonsils in the rheumatic.

Though we are so convinced of the importance of the tonsils as an avenue of infection, we are alive to the fact that even enucleation does not prevent further attacks of acute rheumatism. The exact value of this operation, and it is the only rational one in our opinion, has still to be estimated by a laborious collection of statistical facts.

The general impression we have gained up to the present time is that the removal of these unhealthy tonsils improves the general health and diminishes the liability to attacks of sore throat. It is not, however, surprising when we realise the minute size of these diplococci that even when the tonsils have been removed, sore throats may occur, for there is ample opportunity for the micrococci to flourish in the faucial tissues or in the hypertrophied mucous membrane of the naso-pharynx, and in such cases we have seen a diffuse red flush over the soft palate and around the pillars of the fauces. Some tenderness and swelling of the cervical lymphatic glands is frequently complained of by the rheumatic.

One of the most frequent combinations of symptoms in acute rheumatism is sore throat, arthritis and morbus cordis, and in severe cases the rheumatic symptoms appear within a week from the commencement of the sore throat.

Rheumatic pleurisy is frequent in severe cases of cardiac rheumatism, and often accounts for some of the thoracic pain in the attacks. Pleuro-pericarditis also is not uncommon. In only exceptional cases is there sufficient sero-fibrinous exudation to require paracentesis.

An unusual and abrupt rise of temperature in the course of an attack of rheumatism, though always suggesting the possibility of hyperpyrexia, may be also the result of a rheumatic *broncho-pneumonia*. This lesion is accompanied by a

good deal of alveolar collapse around, and may thus give rise to very definite signs of pneumonia, although the actual area involved is usually small. In virulent cases there may be numerous patches of this kind.

Acute pulmonary œdema we have only seen with severe carditis. Sharp râles appear over the upper parts of the lungs, and spreading rapidly may involve all the lobes. Lividity, rapid breathing and heart failure usually develop, but with free stimulation and the administration of atropine there may be an arrest in the spread of the œdema, and recovery may follow. The proof of this lesion rests on careful post-mortem and microscopic investigations, but it is certainly a very rare event, which we ourselves have only met with in childhood.

Although Hirsch and others have recorded rheumatism of the crico-arytenoid joints with *laryngitis* we have not had an opportunity of observing such a case and have not been able to recognise with certainty a rheumatic *bronchitis*.

The *thyroid* has attracted considerable attention in acute rheumatism, but definite facts are difficult to obtain. Thyroiditis has been recorded, and we have occasionally seen some fullness with tenderness of the gland during chorea in childhood. The association of exophthalmic goître with a previous history of rheumatism is well recognised, but it is difficult to trace the sequence of events. We have never seen any case of this kind arise in childhood during or after acute rheumatism.

Ocular changes. The chief lesions are conjunctivitis, both erythematous and phlyctenular, and iridocyclitis, which is certainly rare.

Cutaneous manifestations. These may occur before the full picture of the disease has developed or during the attack, or as an almost solitary incident between definite attacks.

Erythemata, scarlatiniform, or more blotchy in character are not infrequent. Sometimes they are very transitory and curiously localised, at other times diffuse, and then may last for some days. In the generalised cases the eruption is often multiform, and some areas of it may be by no means unlike a tinea circinata or erythema iris. Blotchy eruptions on the face may be difficult of diagnosis if the history of the case is unknown. Purpura as one of our papers illustrates may be severe and widespread, but the occurrence is rare. Purpuric eruptions of slight severity are far more common, and every

gradation from an erythema to a purpura may be noticed in a single case. Heat applied to a rheumatic erythema, or the stress of gravity upon the dilated capillaries may convert such an erythema into a purpura. Branny desquamation may follow the most acute erythemata.

Psoriasis appears to us, as it did to the late Dr. Crocker, to bear some relation to rheumatism, and may possibly represent the more chronic type of rheumatic manifestation in the skin. *Bullous* eruptions are rare, *herpetic* ones rather more frequent. It is worth consideration whether the so-called *sudaminal* eruption is not in reality a rheumatic manifestation.

Erythema nodosum is a condition of much interest and one about which there is no agreement as to causation. It may occur in the rheumatic and it may also occur in those who have never had rheumatism. Whether it is a special disease allied to acute rheumatism or whether it is an outcome of many different infections, including among these the rheumatic, is not decided.

Scleroderma is occasionally met with after an attack of rheumatic fever.

The blood is much damaged by virulent rheumatism and the late Dr. Cheadle frequently pointed out that in childhood it suffered almost as much in this disease as in severe diphtheria. There is a rapid fall in the number of red cells, and the count may remain very persistently low. A moderate leucocytosis may also occur. The diplococcus can be isolated from the blood in virulent cases, and we have demonstrated their presence in the polymorphonuclear leucocytes.

Nephritis and other renal lesions deserve notice. The acute condition is generally transitory; but there is a persistent form associated with some cases of malignant rheumatic endocarditis that seems to us to require more attention than it has received. There may also be transient albuminuria. Further, our experimental investigations show that renal infarction may occur with no visible endocardial lesions, which raises the question as to whether our present views on the pathology of infarction are not somewhat too rigid in their conception.

The association of chronic renal disease with mitral stenosis has already been alluded to, and also needs further investigation. In twenty fatal cases of mitral stenosis, all of which

showed granular kidneys, the age limits varied between 19 and 60 years, and seventeen of these were under fifty years of age.

The abdominal symptoms in rheumatism are another field for further investigation, and at present difficult to write upon with any confidence.

Children of rheumatic parentage are liable to attacks of bilious vomiting with white constipated stools, and at the commencement of an acute attack, vomiting and diarrhœa with much mucus in the stools may occur. Again, between attacks of acute rheumatism mucous colitis may develop. In adults severe gastric pain with vomiting and dilatation, or attacks of pain along the colon, may add greatly to the severity of the disease.

What relation, if any, the muco-membranous colitis of the adult bears to rheumatism is uncertain.

We isolated the diplococcus, which was sometimes growing in great numbers, from the *bile* in infected rabbits on more than one occasion, but heretofore have failed with cultures from the human bile. The subject is, nevertheless, worth some further consideration as having a possible bearing upon the formation of gall-stones, and as a reminder that the liver may, for all we know to the contrary, be affected by the rheumatic poisons.

Beattie has directed attention to the precipitation of bile salts by the diplococcus *in vitro*, and we have observed the occurrence of a large *gall-stone* in a rabbit which had been inoculated intravenously with this micro-organism.

Appendicitis has been already dealt with in several of our papers, but the clinical points of chief interest at the moment are as to whether or not we shall in the future be able to recognise a relapsing rheumatic form of the affection, or whether the relation of rheumatism and appendicitis, so clear from animal experiment, does not hold good in man.

Peritonitis undoubtedly occurs as a rheumatic lesion, but it is exceptional. The usual symptoms are pain in the upper half of the abdomen, and loud peritoneal friction may be heard. The inflammation is usually around the spleen and over the liver, but cases of general peritonitis have been described, fibrinoplastic in character, and we have seen general peritonitis result from experiment.

Fever. There is no special course in the pyrexia, but there are several interesting clinical facts about the fever in rheumatism. The remarkable phenomenon of hyperpyrexia is the best known, but it is very rare at the present time, and in childhood a very unusual event indeed. Many cases of rheumatism run a course of moderate fever (102° F.) terminating by lysis ; others may show many recrudescences extending over weeks. A severe lesion such as pericarditis or a pneumonia, may cause an abrupt rise, but this is seldom alarming.

The virulent cases may show very little fever, or even a subnormal variation.

There are cases in childhood in which some fever may continue over many weeks with no obvious clinical sign to account for it. This may be only of slight degree, but experienced physicians regard this fever with suspicion, and there is no sense of real security while it persists. This fact, proved by observation in hospital wards, is of particular importance because it is also recognised that the only evidence of rheumatism may sometimes be a mysterious and persistent fever ; and the definite manifestations only appear later.

There would seem to be room for further observation upon the possible effect of the rheumatic infection upon the *reproductive system.*

We have observed, as has Dr. Still, *mastitis* of a mild form occurring occasionally in girls of 10 to 12 years of age, who have been the subjects of rheumatic fever ; but this may well have been a coincidence. *Dysmenorrhœa* of an acutely painful nature may also occur in girls with a rheumatic history, yet this, though interesting, is only suggestive, and may quite well be independent of any definite lesions of a rheumatic kind.

The influence of the *puerperium* upon attacks of rheumatism has seemed to us to be detrimental and to favour the development of persistent and sometimes malignant lesions of the cardiac, arthritic and nervous systems.

Attention has been already drawn to the possible influences upon rheumatic manifestations of altered conditions of life and surroundings, faulty habits and advancing age.

DIAGNOSIS AND PROGNOSIS

(*a*) DIAGNOSIS

THE nature of the rheumatic infection both helps us to realise and prepares us for the difficulties that may arise in diagnosis. The micrococcus is itself one of a primitive and large group of bacteria, with close allies such as the pneumococcus and more septic streptococci. The lesions it produces are numerous and may occur in groups or singly, and each one may be mild or severe in character.

It is easily understood then why many have claimed that acute rheumatism is not in reality a specific disease but a result of various infections ; but none the less we hold that this view is mainly held by those who have limited their observations to a study of the disease in the adult. Acute rheumatism is, in fact, one of the most specific diseases in this country ; but for the reasons given above the clinical difficulties in diagnosis are often very great.

As is the case with other infections the diagnosis is most evident when the complete picture is presented by the disease in a severe attack with many manifestations. It is then that we recognise the association with tonsillitis, the liability to cardiac injuries, the absence of suppuration, the occurrence of a transient painful polyarthritis, of subcutaneous nodules, erythemata and anæmia, and the frequency of exacerbations.

When only one or a few manifestations are present or when the disease is unusually prolonged or more "septic" in character doubts may arise.

It is exceedingly difficult to enumerate all the possibilities of error in the diagnosis, but a comparatively easy matter to classify them.

A solitary symptom such as pain in the limbs accounts for many, particularly if with it is combined the practical difficulty

that is experienced by the medical man in meeting the demand of the public for a name for all disorders.

Here, for example, we should put in childhood, scurvy, osteo-myelitis and anterior poliomyelitis, in the adult the lightning pains of locomotor ataxy or neuritic pains of carcinoma of the vertebræ. With the mistake of relying upon one sign we often find we have coupled that of imperfect observation, and have missed the tender swellings of scurvy, the extreme illness of osteo-myelitis and the loss of reflexes in polio-myelitis.

Another source of numerous errors is failure in realising that there are many infections which may cause a particular lesion such as arthritis, and that the clinical signs of an early arthritis furnish but comparatively crude data for the differentiation of its causation.

Here we group the errors of mistaking for rheumatism, gonorrhœal, septic, tubercular, pneumococcal, syphilitic and other forms of arthritis. This is an error all the more easily made because the term rheumatism is used vaguely, sometimes for a special disease and sometimes for a transitory arthritis. Here again imperfect observation encourages error from the oversight of the other manifestations of each of these diseases, some of which, when coupled with the arthritis, would make the diagnosis clear.

A third group of errors arises from the limitations of our knowledge. This is illustrated by "rheumatoid arthritis." Our views on this condition are even now in a state of chaos partly from a lack of accurate facts about the bacteriology and also from ignorance of the possibilities the metabolic changes in the tissues themselves may possess for producing disease without the aid of infection. The difficulties are increased by the continual appearance of dogmatic assertions as to the nature of the condition.

It is clear that if some specific test could be found for the diplococcus, the problem of the diagnosis of acute rheumatism would be greatly simplified.

(*b*) PROGNOSIS

The conception of acute rheumatism as the result of an infection undoubtedly gives much assistance in prognosis, for when we accept it, we naturally find ourselves guided

by the rules which govern our thoughts upon infective processes in general. We attempt instinctively to gauge the virulence of the infection guided by the clinical evidences of that virulence, and we also pay attention to the individual attacked ; ascertain his family history and apprise his power of resistance by the general rules which guide us in all such inquiries. Age, surroundings, and other predisposing influences are also taken into account.

Yet these general indications are not the only guides. We have also the assistance afforded by the study of the infection in those organs which are most affected in the particular illness.

It is clear that a delicate child of tender age with a strong hereditary predisposition to the disease, who is struck down by acute rheumatic fever with severe carditis will either die or be so crippled that in the future the health will be greatly damaged.

We recognise even more than this, however, for we realize that such a patient, far from being protected from future attacks is exceedingly liable to them.

On the other hand, a strong adult with an attack of severe polyarthritis, brought on by exceptional exposure to adverse influences, will in all probability make a good recovery, and although liable in the future to renewed attacks may, if he is prudent, never suffer again.

Again we are brought to realise a very difficult problem in the prognosis in early life which is dependent upon the tendency of the disease to recur. This turns on the unfortunate fact that because a child has escaped on one occasion with little or no damage it is, nevertheless, no guide as to the possible severity of a future attack.

This problem is clearly one upon which in the future persistent study of the disease as a result of infection will probably throw light.

We are, however, not only guided in our prognosis by the virulence of the infection, but also by the particular character of the process. When the chronic smouldering form discloses itself, as for example, in the advent of a mitral stenosis, we recognise that such damage as has been done is permanent, and, moreover, exceedingly likely to progress, although perhaps very slowly.

When we turn to the particular organ affected, with the

rare exceptions of fatal chorea or hyperpyrexia, it is brought home to us that the heart is the great danger point. Here again we gain great assistance in prognosis. Severe carditis, damaging as it does several valves, the heart wall and pericardium, must always be grave. Malignant types of endocarditis, by virtue of their peculiar relation to the general circulation, are nearly always fatal. The great importance of damage to the myocardium is brought home to us as a common result of cardiac infections, and we can understand how it may be that a simple mitral endocarditis, which would seem to be the least dangerous of valvular lesions may, nevertheless, run a most disastrous course because the rheumatic infection has at the same time greatly injured the cardiac wall.

The influences of imperfect convalescence, poverty, unhealthy surroundings and laborious occupations can be thoroughly realised as tending to cause renewed cardiac injury.

A knowledge of the morbid changes that occur in arthritis speedily makes us alive to the gravity of persistent inflammation in these structures and helps us to recognise the extent which we may expect the limits of recovery to reach.

So also our knowledge of the pathology of rheumatic chorea lead us to understand the recovery which we may expect, although it may be long delayed.

Enough, we think then, has been written upon this question of prognosis in rheumatism to make it apparent how helpful the view of the disease we have put forward is in solving its various difficulties, and keeping before us the limitations of our knowledge.

TREATMENT

THE last consideration is the influence of these researches upon the all-important problem of the treatment of the disease.

As we have stated in the introduction, no dramatic "Cure" has appeared to encourage us, but on the contrary the specific treatment has seemed to become an even more difficult problem than it was before we commenced these investigations. How we are to destroy these micrococci in the tissues without at the same time injuring the tissues themselves is the obvious difficulty that confronts us, and is the greater because they may have gained a firm hold in the system before any opportunity of coping with them is afforded. Then, owing to the extreme difficulty of differentiating the members of the streptococcal group, and the difficulty we have found in preserving the virulence of the diplococcus *in vitro*, a study of the toxines has been an undertaking beyond our powers. Further clinical investigation of the results of this infection has brought home to us the extreme subtlety of the poisons that are produced which may cause prolonged and most complex results in such organs as the brain, where the clinical results can be so clearly recognised.

Many of the methods of treatment that are described in every text-book can be readily seen to be rational, such as rest, the relief of pain, the combating of fever, and the prolonged convalescence, for they are measures needful in the treatment of all infections, and the slow convalescence is particularly called for by the peculiar tendency of the rheumatic infection to attack the heart. Our researches obviously suggest great attention to sore throat during the illness.

With more caution as to the interpretation, the employment of the alkalis would appear to be of value, for the little that is known of the poisons produced by the diplococcus points to

the production of deleterious acids as one of its results in the tissues.

The great problem every medical man meets with in the matter of drugs is, we need hardly state, the position of the salicyl-compounds in the treatment of the disease; and upon it we write with the utmost deference to the opinions of others. No thinking man, with a knowledge of the ravages of rheumatism before his mind, would deliberately attempt to obstruct any method of treatment of this disease which promised to be specific, and nothing that is written here should be looked upon as an expression of an antagonistic attitude to those who are not in agreement, but as an expression of opinion based upon what appears to us the present evidence.

To us it has seemed astonishing, when we bear in mind the immense experience of these drugs that has now accumulated, that the specific action if it exists has not yet been definitely established. We look upon a specific drug as one which produces results so definite and incontestable that none but the blind opponent can mistake them. Our experience has been that whether very large, medium or small doses of the salicylates are given in this disease, we have failed to discover any such striking results. We would put a clear issue forward and state that if ten cases of acute rheumatism in which subcutaneous nodules were appearing were treated by any doses of these drugs that a physician chose to venture, and ten more were treated by the simple alkalis, the result would be that we should see no striking difference in their course under the two methods. That is, although they are the most easily appreciated and most characteristic of all rheumatic lesions, we should not see them melt away under the salicylate treatment and linger under the alkaline.

We cannot deny that the salicylates relieve pain, and lower the temperature, but they do this, it must be added, in many other conditions. Aspirin will relieve the pain of cancer, of tabes dorsalis and of influenza. Salicylate of soda will ease the pain of gout and of early suppurative arthritis. Whenever there is relief of pain there is mental and bodily rest, and consequently more vital power for the natural resistance to diseased processes.

It is quite possible that these drugs may have some actual

specific influence upon the rheumatic poisons formed in the processes of arthritis, and not upon the poisons formed in different tissues such as the brain and heart. Even this point, however, does not seem to stand out clearly, for it is remarkable how rapidly in childhood a rheumatic arthritis will subside when only rest is employed; and on the other hand, when in an adult or child the arthritis is of the stubborn periarticular type, how the salicylates may fail. The obvious objection that is always raised is that these latter cases are not rheumatic. We can only state that our experience has led us to maintain that they are undoubtedly of that nature, and would add that we believe that in some delicate subjects these drugs, if persisted in, do actual harm by producing a general depression of the resistance. It is worthy of consideration also, whether these drugs, by lowering temperature and easing pain, may not sometimes lull the medical man into a sense of false security.

We would wish to make it quite clear that these expressions of opinion are concerned only with the specific action of the salicylates. We realise the great value of these drugs in the treatment of rheumatism and look upon them as the most valuable that we possess, and even think that they may have a specific action on some one of the rheumatic poisons; but fully alive as we are to their value we would point out that they are most efficacious in those cases which are acute and in which pain and suffering with fever are prominent, and in which the lesion is the most transitory and most easily produced of all the rheumatic manifestations, namely polyarthritis.

The natural conclusion is that we advocate their use for the polyarthritis, muscular pains, or headache of chorea, but do not press them for their specific action in heart disease, although prepared to do so tentatively in severe polyarthritis. We do not press them in heart disease or chorea, because not being persuaded of their specific action, we are convinced from experience that they may produce severe vomiting, general depression, dizziness, delirium, air-hunger and even fatal coma. In other words they may introduce into severe cases, added dangers of their own making.

The various tonics used in the convalescent stages of the disease require no particular comment, except that the digestion

of these patients is by no means always satisfactory and caution is needed in giving the iron compounds.

The question of diet is an interesting one, and all our investigations go to show that in childhood it takes no part in causation of the disease. We have entirely abandoned the idea that meat is harmful, and are guided only by the general rules for the diet of invalids dependent upon their powers of assimilation, the stage of the disease and the occurrence or not of complications.

It is another question whether persistent errors in diet may not in the adult deprave the tissues and allow the rheumatic infection to produce lesions which are more locally destructive than in the child. In this case it is the evil habit of life that has altered the constitution before the infection has attacked the individual.

The *treatment by vaccines* will, in this country, be the one in which we should expect the medical profession will show particular interest, but we would raise a mild protest against an argument that has been raised of late, that failure with this method is strong evidence against the causal nature of the diplococcus. This is indeed a questionable method of reasoning, for it assumes that the vaccine methods are perfected and that their method of action is well understood. Upon these assumptions obvious and indisputable facts of experimental investigation are to be thrown aside.

By this method of treatment good results and negative results have been recorded, and both events would seem to be possible.

It must, however, be remembered that rheumatism is a very difficult disease in which to estimate the value of curative measures, and the real truth can only be obtained by laborious investigation and the most open statement of all facts. It is not to be supposed that the pain of the rheumatic lesions will be speedily quelled by this method, and this will in many cases involve the employment of the salicylates which must greatly embarrass the case when viewed by the believers in the specific action of these drugs.

Our experience has been so far very unconvincing but we have learnt this practical point, that if these vaccines are potent for good, they need to be used very cautiously where there are active cardiac lesions, and we would warn against

the wild use of large doses simply because these methods are so much in vogue. We ourselves commence with the dose of 1,000,000 and find our way cautiously forward.

The serum treatment presents also great difficulties connected with the rapid loss of virulence of the micrococcus, and has been unsatisfactory. Yet it would be very unwise to express formed opinions upon either method, which are in their infancy and which may in the future vastly improve with increasing knowledge.

THE PREVENTION OF ACUTE RHEUMATISM

THE possibility of doing more for the prevention of this disease than has been accomplished heretofore has been the main purpose of our investigations.

We believe it to be one of the great undertakings in the medical history of this country.

The importance of the prevention of an infection which is the great cause of organic heart affections in the young is one that cannot be over-rated; and we believe that definite results will be forthcoming because acute rheumatism is met with much more frequently among the poorer classes and is encouraged by those agencies, which may be summed up in the single word "poverty."

We are now, we believe, in a position to study the prevention of this disease guided by a definite and reasonable working hypothesis, and one which though it exposes our limitations is in the main an encouraging one.

The changeable climate and seasons of this country are elements beyond our control, and must be taken into account in the problem of prevention as baffling influences. Nevertheless, that these agencies are not wholly responsible for the frequency of the disease is clear from its greater incidence upon the poorer classes.

In the great hospitals it is clear that we possess ample means for treating the acute disease and its complications and for advancing its study in many directions. Their value might well be strengthened in the future by the establishment of some special convalescent homes in carefully chosen sites for those recovering from early rheumatism including heart disease and chorea. In our experience the ordinary convalescent home is not suited for such cases, particularly when they are children, for they need constant medical supervision and nursing.

We are convinced that the medical inspection of children in the State schools will in the near future provide us with valuable information upon the influence of school-life on

chronic rheumatic heart disease and on the relation of outbreaks of acute rheumatism to epidemics of sore throats. It may perhaps be hardly realised how great a loss of time and educational energy is due to chorea : many children as the result of this illness may lose as much as three months' education each year for some years in succession. It is possible that careful inquiry may discover that there is some factor in our present methods of education which introduce too great a strain or perhaps throw a peculiar strain upon the developing brain of these children. In support of the importance of the medical inspection of school children, we would quote from the annual report for 1911, of the Chief Medical Officer of the Board of Education, Sir George Newman, the following sentence : "School inspection provides a wide field for inquiry and research, and many opportunities of bringing home the danger of neglecting evidences of rheumatism however slight in degree." This sentence expresses concisely the important, indeed indispensable, assistance that can be given by the school medical officers.

The education of parents and school-teachers in the principal dangers of acute rheumatism might well be carried on by means of simple instructions and lectures. Among such instructions may be suggested the following for rheumatic children.

1. The importance of proper clothing.
2. The care of sore throats.
3. The necessity for attention to "growing-pains."
4. The importance of undue nervousness, clumsiness, and night-terrors as warnings of chorea.
5. Parents should be warned that the early signs of heart disease are few, and that shortness of breath is more often complained of than pain.
6. Much emphasis should be laid upon need for patience when a child is recovering from heart disease.
7. Parents should be told that rheumatism is very liable to recur.

We believe that more attention might be given to the condition of the tonsils and naso-pharynx in the rheumatic child, and also to the choice of an employment for those who have been damaged by the disease.

The view that acute rheumatism is an infective disease raises

again the important questions of climatic and local surroundings, sanitation and conditions of housing. The possible relation that it may bear to other infective processes such as scarlet fever, measles, diphtheria, influenza, or even tuberculosis seems worthy of further inquiry, more particularly as in some of these diseases a sore throat is a prominent symptom. Investigations in these directions would, we believe, give further assistance in dealing with the problem of prevention, and come into the province of the Medical Officers of Health.

We are convinced that the general subject of "Rheumatism" has only reached the threshold of inquiry, and that in every direction new fields for research and inquiry are before us.

In conclusion, this is certain; that at the present time, in spite of all that has been written upon the treatment of acute rheumatism, there are hundreds of young children who are so damaged by this disease that all known methods of "cure" are utterly useless to them. It is to *prevention*, then, that we look for some advance from this grievous state of affairs, and it is with the desire of directing the attention of our profession to this pressing need that we have ventured to publish this book, in the hope that it may have some influence toward achieving this end.

INDEX

BALLANTYNE & COMPANY LTD
Tavistock Street Covent Garden
London

No. 4.

J. & A. CHURCHILL

Recent Works for Students and Practitioners of Medicine.

LONDON:

7, Great Marlborough Street.

MARCH, 1913.

INDEX.

FREE ON . . . APPLICATION.

1. Complete Illustrated Catalogue.
2. Catalogue of Science Books.

Anatomy & Physiology

A Treatise on Human Anatomy. By various Authors. Edited by Sir Henry Morris, Bart., M.A., F.R.C.S.; and J. Playfair McMurrich, A.M., Ph.D., Professor of Anatomy, University of Toronto. Fourth Edition. With 1025 Engravings, of which 319 are printed in 3 or 4 colours. 30*s.* net. Also issued in 5 parts. Parts I, II, and III, 8*s.* net each; and Parts IV and V, 5*s.* net each.

Anatomical Terminology, with Special Reference to the B.N.A. By L. F. Barker, M.D., Professor of Medicine, Johns Hopkins University. With Illustrations. 5*s.* net.

A Manual of Practical Anatomy. By the late Professor Alfred W. Hughes, M.B., M.C.Edin., Professor of Anatomy, King's College, London. Edited and completed by Arthur Keith, M.D., Lecturer on Anatomy, London Hospital Medical College. In three parts, Part I, 10*s.* 6*d.* Part II, 8*s.* 6*d.* Part III, 10*s.* 6*d.*

Heath's Practical Anatomy: a Manual of Dissections. Edited by J. E. Lane, F.R.C.S., Surgeon and Lecturer on Anatomy at St. Mary's Hospital. Ninth Edition. 321 Engravings. 12*s.* 6*d.*

Clinical Applied Anatomy; or, The Anatomy of Medicine and Surgery. By Charles R. Box, M.D., F.R.C.P.Lond., Physician to Out-patients, St. Thomas's Hospital, and W. McAdam Eccles, M.S.Lond., F.R.C.S.Eng., Surgeon, with charge of Out-patients, St. Bartholomew's Hospital. Illustrated by 45 Plates. 12*s.* 6*d.* net.

Essentials of Surface Anatomy. By Charles R. Whittaker, F.R.C.S., L.R.C.P., etc., Demonstrator of Anatomy, Surgeons' Hall, Edinburgh. Second Edition. With 12 Plates, containing 20 Figures, many in Colours. 3*s.* 6*d.* net.

Text-Book of Anatomy and Physiology for Nurses. By Elizabeth R. Bundy, M.D. Second Edition. With a Glossary and 215 Illustrations (42 in Colours). 7*s.* 6*d.* net.

Human Osteology. By Luther Holden. Eighth Edition. Edited by Charles Stewart, F.R.S., and Robert W. Reid, M.D., F.R.C.S. 59 Lithographic Plates and 74 Engravings. 16*s.* **Landmarks, Medical and Surgical.** Fourth Edition. 3*s.* 6*d.*

Principles of Human Physiology. By Ernest H. Starling, M.D., F.R.C.P., F.R.S., Jodrell Professor of Physiology, University College, London. 564 Illustrations. 21*s.* net.

BY THE SAME AUTHOR.

Elements of Human Physiology. Eighth Edition. 323 Illustrations. 12*s.* 6*d.* net.

A Course of Experimental Physiology. By N. H. Alcock, M.D., Prof. Physiol. McGill Univ.: and F. O'Brien Ellison, M.D., B.A.O.Dub., St. Mary's Hospital. 36 Illustrations. 5*s.* net.

Practical Physiological Chemistry. By Philip B. Hawk, M.S., Ph.D., Professor of Physiological Chemistry in the University of Illinois. Third Edition. With Coloured Plates and 127 Figures. 16*s.* net.

The Cell as the Unit of Life, and other Lectures: An Introduction to Biology. By the late Allan Macfadyen, M.D., B.Sc., Fullerian Professor of Physiology, Royal Institution, London. Edited by R. Tanner Hewlett, M.D., F.R.C.P., D.P.H. 7*s.* 6*d.* net.

The Functional Inertia of Living Matter. By David Fraser Harris, M.D., C.M., B.Sc.(Lond.), F.R.S.E., Physiological Department, University of Birmingham. 12 Illustrations. 5*s.* net.

Materia Medica & Pharmacy

A Text-Book of Pharmacology and Therapeutics, or the Action of Drugs in Health and Disease. By Arthur R. Cushny, M.A., M.D., F.R.S., Professor of Pharmacology in the University of London, etc. Fifth Edition. 61 Illustrations. 15*s.* net.

Materia Medica, Pharmacy, Pharmacology, and Therapeutics. By W. Hale White, M.D., F.R.C.P., Physician to, and Lecturer on Medicine at, Guy's Hospital. Twelfth Edition. 6*s.* 6*d.* net.

A Text-Book of Materia Medica for Students of Medicine. By C. R. Marshall, M.D., Professor of Materia Medica, University of St Andrews. 127 Illustrations. 10*s.* 6*d.* net. **A Manual of Prescribing for Students and Practitioners.** 5*s.* net.

Southall's Organic Materia Medica. By John Barclay, B.Sc.Lond. Seventh Edition by E. W. Mann. 7*s.* 6*d.* net.

A Text-Book of Materia Medica. By Henry G. Greenish, F.I.C., F.L.S., Professor of Pharmaceutics to the Pharmaceutical Society. Second Edition. 269 Illustrations. 15*s.* net. **The Microscopical Examination of Foods and Drugs, in the Entire, Crushed, and Powdered States.** Second Edition. 209 Illustrations. 12*s.* 6*d.* net. **An Anatomical Atlas of Vegetable Powders.** 138 Illustrations. 12*s.* 6*d.* net.

Materia Medica, Step by Step. By A. W. Nunn. 3*s.* 6*d.* net.

Practical Pharmacy. By E. W. Lucas, F.I.C., F.C.S. Second Edition. 224 Illustrations. 12*s.* 6*d.* net.

BY THE SAME AUTHOR.

The Book of Prescriptions (Beasley) with an Index of Diseases and Remedies. Ninth Edition. 6*s.* net.

The Book of Receipts: containing a Veterinary Materia Medica, a Pharmaceutical Formulary, a Photographic Formulary, a Synopsis of Practical Methods employed in the Examination of Urine, Milk, Potable Waters, Sputum, etc. With 10 Plates. 7*s.* 6*d.* net.

First Lines in Dispensing. 93 Illustrations. 3*s.* 6*d.* net.

The National Standard Dispensatory. By H. A. Hare, B.Sc., M.D., and others. Second Edition. 478 Illustrations. 36*s.* net.

Medical and Pharmaceutical Latin for Students of Pharmacy and Medicine. By Reginald R. Bennett, Pharmacist and Teacher of Pharmacy at University College Hospital, London. 6*s.* net.

A Companion to the British Pharmacopœia. By Peter Wyatt Squire, F.L.S., F.C.S. Eighteenth Edition. 14*s.* net. **Pocket Edition.** 7*s.* 6*d.* net. **The Pharmacopœias of Thirty of the London Hospitals.** Arranged in Groups for comparison. Eighth Edition. 5*s.* net.

The Pharmaceutical Formulary: a Synopsis of the British and Foreign Pharmacopœias. By Henry Beasley. Twelfth Edition by J. Oldham Braithwaite. 6*s.* 6*d.*

Tuson's Veterinary Pharmacopœia. Sixth Edition. Edited by James Bayne, F.C.S. 7*s.* 6*d.* net.

Year-Book of Pharmacy. Annually, 10*s.* net.

Hygiene & Bacteriology

The Theory and Practice of Hygiene. (Notter and Firth.) By R. H. Firth, Lt.-Col. R.A.M.C., F.R.C.S., Officer in Charge of the School of Army Sanitation, Aldershot. Third Edition. 22 Plates (some in colours) and 200 other Illustrations. 21*s.* net.

BY THE SAME AUTHOR.

Military Hygiene: a Manual of Sanitation for Soldiers. With 40 Illustrations. 3*s.* 6*d.* net.

Manual of Hygiene. By W. H. Hamer, M.D., Lecturer on Public Health, St. Bartholomew's Hospital. 93 Illustrations. 12*s.* 6*d.* net.

Lessons on Elementary Hygiene and Sanitation, with Special Reference to the Tropics. By W. T. Prout, C.M.G., M.B., C.M.(Edin.), Hon. Lecturer School of Tropical Medicine, Liverpool. Third Edition. In Preparation.

Domestic Hygiene for Nurses. By Fred J. Smith, M.D., F.R.C.P., Physician to London Hospital. 18 Illustrations. 2*s.* 6*d.* net.

The Effects of Borax and Boric Acid on the Human System. Third Treatise. By Dr. Oscar Liebreich. 5*s.* net.

The Action of Boron Preservatives on Bacillus Coli and Allied Microbes. By E. Klein, M.D., F.R.S., Lecturer on Advanced Bacteriology, St. Bartholomew's Hospital. 6*d.* net.

A Simple Method of Water Analysis. By John C. Thresh, M.D.Vic., D.Sc.Lond. Seventh Edition. 2*s.* 6*d.* net.

BY THE SAME AUTHOR.

The Examination of Waters and Water Supplies. 19 Plates and 11 Figures in the Text. Second Edition. Nearly Ready.

ALSO, WITH ARTHUR E. PORTER, M.D., M.A.CANTAB.

Preservatives in Food and Food Examination. 8 Plates. 14*s.* net.

Foods and their Adulteration. By Harvey W. Wiley, M.D., Ph.D. Second Edition. With 11 Coloured Plates and 87 other Illustrations. 21*s.* net.

Text-book of Meat Hygiene, with Special Con- sideration of Ante-mortem and Post-mortem Inspection of Food-producing Animals. By R. Edelmann, Ph.D., Professor, Royal Veterinary High School, Dresden. Translated by J. R. Mohler, A.M., V.M.D., and A. Eichhorn, D.V.S. With 152 Illustrations and 5 Coloured Plates. 21*s.* net.

A Manual of Bacteriology, Clinical and Applied. By R. Tanner Hewlett, M.D., Professor of General Pathology and Bacteriology in King's College, London. Fourth Edition. 26 Plates and 69 Figures in the Text. 10*s.* 6*d.* net.

BY THE SAME AUTHOR.

Serum and Vaccine Therapy, Bacterial Thera- peutics and Prophylaxis, Bacterial Diagnostic Agents. Second Edition. 32 Figures. 7*s.* 6*d.* net.

Clinical Diagnostic Bacteriology, including Serum- and Cyto-diagnosis. By Alfred C. Coles, M.D., D.Sc., F.R.S.E. 2 Coloured Plates. 8*s.* net.

Lessons in Disinfection and Sterilisation. By F. W. Andrewes, M.D., F.R.C.P., Lecturer on Pathology, St. Bartholomew's Hospital. Second Edition. 31 Illustrations. 3*s.* 6*d.* net.

Pathology & Psychology Dictionaries

Pathology, General and Special, for Students of Medicine. By R. Tanner Hewlett, M.D., F.R.C.P., D.P.H., Professor of General Pathology and Bacteriology in King's College, London. 32 Plates and 15 Illustrations in Text. Third Edition. 10s. 6d. net.

Clinical Pathology. By P. N. Panton, M.B., Clinical Pathologist and Director of Hale Clinical Laboratory, London Hospital. With 11 Coloured Plates and 48 Text-figures. *Ready May*, 1913.

Manual of Pathology, including Bacteriology, the Technic of Post-mortems, etc. By W. M. L. Coplin, M.D., Professor of Pathology, Jefferson Medical College, Philadelphia. Fifth Edition. With 612 Illustrations and 12 Plates. 21s. net.

A Manual of General or Experimental Pathology. By W. S. Lazarus-Barlow, M.D., F.R.C.P., Director of the Cancer Research Laboratories, Middlesex Hospital. Second Edition. 21s. net. **The Elements of Pathological Anatomy and Histology for Students.** 24s. net.

Surgical Pathology and Morbid Anatomy. See p. 8.

Manual of Clinical Pathology. By R. Weiss, M.A., Ph.D., F.C.S., G. Herschell, M.D., and A. Charles, F.R.C.S. 16 Illustrations. 2s. net. **Nurses' Clinical Pathology.** Second Edition. 1s. net.

Post-mortem Manual. By C. R. Box, M.D., Lecturer on Applied Anatomy, St. Thomas's Hospital. 19 Illustrations. 6s. net.

The Pathologist's Handbook: a Manual for the Post-mortem Room. By T. N. Kelynack, M.D. 126 Illustrations. 4s. 6d.

Psychological Medicine. By M. Craig, M.D., Physician, Mental Diseases, Guy's Hospital. Second Edition. 27 Plates. 12s. 6d. net.

Mental Diseases: Clinical Lectures. By Sir T. S. Clouston, M.D., F.R.C.P.Edin. Sixth Edition. 30 Plates. 14s. net.

The Force of Mind; or, the Mental Factor in Medicine. By Alfred T. Schofield, M.D., Hon. Physician to Friedenheim Hospital. Third Edition. 5s. net. **Unconscious Therapeutics; or, The Personality of the Physician.** Second Edition. 5s. net. **The Management of a Nerve Patient.** 5s. net.

The Journal of Mental Science. Published Quarterly, by Authority of the Medico-Psychological Association. 5s. net.

Dictionary of Medical Terms: English, French, German. Edited by Paul Blaschke. 8s. net. **Dictionary of Medical Conversation; English-German,** 4s. net. **German-English,** 4s. net.

A German-English Dictionary of Terms used in Medicine and the Allied Sciences. By Hugo Lang, B.A., and Bertram Abrahams, M.B., B.Sc., F.R.C.P. 15s. net.

Dunglison's Dictionary of Medical Science. By Thomas L. Stedman, M.D. Twenty-third Edition. 577 Illustrations, including 84 page-plates. 34s. net.

A Medical Vocabulary. By R. G. Mayne, M.D. Seventh Edition, by W. W. Wagstaffe, F.R.C.S., and G. D. Parker, M.B. 12s. 6d.

Medicine

A Text-Book of Medicine. Begun by the late C. Hilton Fagge, M.D.; completed and re-written by P. H. Pye-Smith, M.D., F.R.S. Fourth Edition. 2 vols. 42*s*.

The Practice of Medicine. By Frederick Taylor, M.D., F.R.C.P., Consulting Physician to, and Lecturer on Medicine at, Guy's Hospital. Ninth Edition. 8 Skiagram Plates and 67 Illustrations. 18*s*. net. **Some Disorders of the Spleen.** 3*s*. net.

A Short Practice of Medicine. By R. A. Fleming, M.D., F.R.C.P.E., F.R.S.E., Lecturer on Medicine, School of Royal Colleges, Edinburgh. Second Edition. 55 Illustrations (7 coloured). 12*s*. 6*d*. net.

The Practice of Medicine. By M. Charteris, M.D. Professor of Therapeutics, University of Glasgow. Ninth Edition. Edited by F. J. Charteris, M.D., Ch.B. Illustrated. 9*s*. 6*d*. net.

A Medical Vademecum, in German and English. By B. Lewis. With a Preface by Prof. Dr. A. Politzer. 15*s*. net.

A Manual of Physical Diagnosis. By B. R. O'Reilly, M.D., M.R.C.S.Eng., Demonstrator in Clinical Medicine, University of Toronto. With 6 Plates and 49 other Illustrations. 8*s*. 6*d*. net.

Digestion and Metabolism: The Physiological and Pathological Chemistry of Nutrition. By A. E. Taylor, M.D., Rush Professor of Physiological Chemistry, University of Pennsylvania. 18*s*. net.

A Dictionary of Medical Treatment. By Arthur Latham, M.D., F.R.C.P., Lecturer on Medicine at St. George's Hospital. 6*s*. 6*d*. net.

Text-Book of Medical Treatment. By N. I. C. Tirard, M.D., F.R.C.P., Professor of Medicine, King's College, London. 15*s*.

A Manual of Family Medicine and Hygiene for India. Published under the Authority of the Government of India. By Sir William J. Moore, K.C.I.E., M.D. Seventh Edition edited by Major J. H. Tull Walsh, I.M.S. 70 Engravings. 6*s*. net.

Waring's Bazaar Medicines of India. By Lt.-Col. C. P. Lukis, I.M.S., Principal of the Medical College, Calcutta. Sixth Edition. 6*s*. net.

The Blood: how to Examine and Diagnose its Diseases. By Alfred C. Coles, M.D., D.Sc., F.R.S.Edin. Third Edition. 7 Coloured Plates. 10*s*. 6*d*. net.

Lectures on Medicine to Nurses. By Herbert E. Cuff, M.D., F.R.C.S., late Medical Superintendent, North-Eastern Fever Hospital, London. Fifth Edition. 29 Illustrations. 3*s*. 6*d*. net.

How to Examine the Chest. By Samuel West, M.D., F.R.C.P., Physician to St. Bartholomew's Hospital. Third Edition. 46 Engravings. 5*s*.

On Alcoholism: Its Clinical Aspects and Treatment. By Francis Hare, M.D., Medical Superintendent of the Norwood Sanatorium, Beckenham. 5*s*. net.

Medicine

A System of Treatment. By many writers. Edited by Arthur Latham, M.A., M.D., F.R.C.P., Physician and Lecturer on Medicine, St. George's Hospital, and T. Crisp English, M.B., B.S., F.R.C.S., Surgeon, St. George's Hospital. In 4 Vols. Vols. I and II. General Medicine and Surgery; Vol. III, Special Subjects; Vol. IV, Obstetrics and Gynæcology. Price £1 1s. net per volume. Detailed prospectus upon application.

Vicious Circles in Disease. By J. B. Hurry, M.A., M.D. Second Edition. With 16 Illustrations. 7s. 6d. net.

Diseases of the Stomach, with Special Reference to Treatment. By C. D. Aaron, Sc.D., M.D., Professor of Gastro-enterology and Professor of Dietetics, Detroit College of Medicine. With 42 Illustrations and 21 Plates. 21s. net.

Ulcer of the Stomach and Duodenum. By Samuel Fenwick, M.D., F.R.C.P., and W. Soltau Fenwick, M.D., B.S. 55 Illustrations. 10s. 6d. **Cancer and other Tumours of the Stomach.** 70 Illustrations. 10s. 6d.

On Carbohydrate Metabolism. By Frederick W. Pavy, M.D., LL.D., F.R.S., F.R.C.P., Consulting Physician to Guy's Hospital. With 8 Plates. 6s. net.

The Schott Methods of the Treatment of Chronic Diseases of the Heart. By W. Bezly Thorne, M.D., M.R.C.P. Fifth Edition. Illustrated. 5s. net.

The Clinical Examination of Urine, with an Atlas of Urinary Deposits. By Lindley Scott, M.A., M.D. 41 original Plates (mostly in colours). 15s. net.

Urine Examination made easy. By T. Carruthers, M.B., Ch.B. Second Edition. 1s. 6d. net.

Electricity: Its Medical and Surgical Applications, including Radio-Therapy and Photo-Therapy. By C. S. Potts, M.D., Professor of Neurology, Medico-Chirurgical College, University of Pennsylvania. With 356 Illustrations and 6 Plates. 18s. net.

Rational Organotherapy. Translated from the Russian Text by Professor Dr. A. von Poehl, Professor Prince J. von Tarchanoff, Dr. Alf von Poehl, and Dr. P. Wachs. Vol. I. 7s. 6d. net.

On Gallstones, or Cholelithiasis. By E. M. Brockbank, M.D.Vict., M.R.C.P.Lond. 7s.

Obstinate Hiccough. By L. F. B. Knuthsen, M.D.Edin. 6s.

On Syphonage and Hydraulic Pressure in the Large Intestine. By Ralph Winnington Leftwich, M.D. 3s. net.

Uric Acid as a Factor in the Causation of Disease. By Alexander Haig, M.D., F.R.C.P., Physician to the Metropolitan Hospital. Seventh Edition. 75 Illustrations. 14s. net. **Uric Acid in the Clinic. A Clinical Appendix to 'Uric Acid as a Factor in the Causation of Disease.'** 5s. net. **Uric Acid, an Epitome of the Subject.** Second Edition. 2s. 6d. net. **Diet and Food considered in relation to Strength and Power of Endurance, Training, and Athletics.** Sixth Edition. 2s. net.

Surgery

The Practice of Surgery. By W. G. Spencer, M.S., F.R.C.S., Surgeon and Lecturer on Surgery, Westminster Hospital, and G. E. Gask, F.R.C.S., Assistant Surgeon and Demonstrator of Practical Surgery, St. Bartholomew's Hospital. 28 Skiagram Plates. 20 Colour Plates. 707 Text-figures. 22*s.* net.

Surgical Pathology and Morbid Anatomy. By Sir Anthony A. Bowlby, F.R.C.S., Surgeon to St. Bartholomew's Hospital, assisted by F. W. Andrewes, M.D., Lecturer on Pathology, St. Bartholomew's Hospital. Sixth Edition. In the Press.

A Manual of Surgical Diagnosis. By James Berry, B.S.Lond., F.R.C.S., Surgeon to, and Lecturer on Surgery at, the Royal Free Hospital. 6*s.* net.

A Synopsis of Surgery. By R. F. Tobin, Surgeon to St. Vincent's Hospital, Dublin. Second Edition. Interleaved, leather binding. 6*s.* 6*d.*

Ovariotomy and Abdominal Surgery. By Harrison Cripps, F.R.C.S., Surgical Staff, St. Bartholomew's Hospital. Numerous Plates. 25*s.*

BY THE SAME AUTHOR.

On Diseases of the Rectum and Anus, including the Fifth Edition of the Jacksonian Prize Essay on Cancer. Third Edition. With 13 Plates and 34 Illustrations. 10*s.* 6*d.* net.

ALSO

Cancer of the Rectum, especially considered with regard to its Surgical Treatment. Jacksonian Prize Essay. Fifth Edition. With 13 Plates and several Engravings. 5*s.* net.

Diseases of the Rectum, Anus, and Sigmoid Colon. By F. Swinford Edwards, F.R.C.S., Senior Surgeon to St. Mark's Hospital for Fistula and other Diseases of the Rectum. Third Edition. 102 Illustrations. 10*s.* 6*d.* net.

A Manual of Minor Surgery and Bandaging. Fourteenth Edition of Heath's. By Bilton Pollard, F.R.C.S., Surgeon to University College Hospital. 250 Engravings. 7*s.* 6*d.* net.

Injuries and Diseases of the Jaws. By Christopher Heath, F.R.C.S. Fourth Edition. Edited by Henry Percy Dean, M.S., F.R.C.S., Assistant Surgeon to the London Hospital. 187 Wood Engravings. 14*s.*

BY THE SAME AUTHOR.

Clinical Lectures on Surgical Subjects delivered at University College Hospital. First Series, 6*s.*; Second Series, 6*s.*

An Essay on the General Principles of the Treatment of Spinal Curvatures. By R. Heather Bigg. Illustrated by Photographs and Sketches. 5*s.* net.

Surgery & Anæsthetics

A System of Treatment. In 4 Vols. By A. Latham and T. Crisp English. See page 7.

The Operations of Surgery. By W. H. A. Jacobson, M.Ch.Oxon., F.R.C.S., Consulting Surgeon Guy's Hospital, and R. P. Rowlands, M.S.Lond., F.R.C.S., Assistant Surgeon, Guy's Hospital. Fifth Edition. 2 vols. 777 Illustrations. 42*s.* net

Hare-Lip and Cleft Palate, with Special Reference to the Operative Treatment and its Results. By James Berry, B.S., F.R.C.S., Senior Surgeon to the Royal Free Hospital, and T. Percy Legg, M.S., F.R.C.S., Surgeon to the Royal Free Hospital. 242 Illustrations and Appendix of Cases. 12*s.* 6*d.* net.

A Treatise on Tumours. By A. E. Hertzler, M.D., Ph.D., Professor of Surgery, University of Kansas. With 538 Engravings and 8 Plates. 30*s.* net.

Practice and Problem in Abdominal Surgery. By Alfred Ernest Maylard, M.B.Lond. and B.S., Senior Surgeon to the Victoria Infirmary, Glasgow. With 39 Illustrations. 8*s.* 6*d.* net.

BY THE SAME AUTHOR.

Abdominal Tuberculosis. 57 Illustrations. 12*s.* 6*d.* net.

Clinical Essays and Lectures. By Howard Marsh, F.R.C.S., Professor of Surgery in the University of Cambridge. 26 Illustrations. 7*s.* 6*d.*

Hernia, its Cause and Treatment. By R. W. Murray, F.R.C.S., Surgeon, David Lewis Northern Hospital. Second Edition. 62 Illustrations. 6*s.* net.

Modern Bullet-Wounds and Modern Treatment, with Special Regard to Long Bones and Joints, Field Appliances and First Aid. By Major F. Smith, D.S.O., R.A.M.C. 3*s.* net.

Surgical Emergencies. By Paul Swain, F.R.C.S., Surgeon to the South Devon and East Cornwall Hospital. Fifth Edition. 149 Engravings. 6*s.*

Chloroform: a Manual for Students and Practi- tioners. By Edward Lawrie, M.B.Edin., Lieut.-Col. I.M.S., Residency Surgeon, Hyderabad. Illustrated. 5*s.* net.

Neurology & Urinary Disorders

A Text-Book of Nervous Diseases. By W. Aldren Turner, M.D., F.R.C.P., Physician and Lecturer on Neurology, King's College Hospital, and T. Grainger Stewart, M.B., M.R.C.P., Assistant Physician, National Hospital for Paralysed and Epileptic. 188 Illustrations. 18*s.* net.

Paralysis and other Nervous Diseases in Childhood and Early Life. By James Taylor, M.D., F.R.C.P., Physician National Hospital for Paralysed and Epileptic, Queen Square. 74 Illustrations. 12*s.* 6*d.* net.

A Manual of Diseases of the Nervous System.
By Sir William R. Gowers, M.D., F.R.S.

Vol. I.—**Nerves and Spinal Cord.** Third Edition, by the Author and James Taylor, M.D., F.R.C.P. 192 Engravings. 15*s.*

BY THE SAME AUTHOR.

Subjective Sensations of Sight and Sound, Abiotrophy, and other Lectures on Diseases of the Nervous System. 18 Illustrations. 6*s.* net.

ALSO

Epilepsy and Other Chronic Convulsive Diseases. their Causes, Symptoms, and Treatment. Second Edition. 10*s.* 6*d.*

ALSO

The Borderland of Epilepsy, Faints, Vagal Attacks, Vertigo, Migraine, Sleep Symptoms, and their Treatment. 4*s.* 6*d.* net.

Text-Book of Nervous Diseases and Psychiatry.
By Charles L. Dana, A.M., M.D., LL.D., Professor of Nervous Diseases in Cornell University Medical College. Seventh Edition. With 3 Plates and 261 Text-figures. 25*s.* net.

Selected Papers on Stone, Prostate, and other Urinary Disorders. By Reginald Harrison, F.R.C.S., Surgeon to St. Peter's Hospital. 15 Illustrations. 5*s.*

By E. Hurry Fenwick, F.R.C.S., Surgeon to the London Hospital.

A Handbook of Clinical Cystoscopy. 31 Plates and 144 Figures in the Text. (*Reprinting.*)

Atlas of Electric Cystoscopy. 34 Coloured Plates. 21*s.* net.

The Value of Radiography in the Diagnosis and Treatment of Urinary Stone. With 80 Plates. 10*s.* 6*d.* net.

Obscure Diseases of the Urethra. 63 Illustrations. 6*s.* 6*d.*

Operative and Inoperative Tumours of the Urinary Bladder. 39 Illustrations. 5*s.* net.

Tumours of the Urinary Bladder. Fasc. I. 5*s.* net.

Ulceration of the Bladder, Simple, Tuberculous, and Malignant: a Clinical Study. Illustrated. 5*s.*

Midwifery & Gynæcology

The Difficulties and Emergencies of Obstetric Practice. By Comyns Berkeley, M.D., F.R.C.P., Obstetric and Gynæcological Surgeon, Middlesex Hospital, and Victor Bonney, M.D., F.R.C.S., Assistant Obstetric and Gynæcological Surgeon, Middlesex Hospital. With 287 Original Illustrations.

The Practice of Midwifery. By A. L. Galabin, M.D., F.R.C.P., and G. F. Blacker, M.D., F.R.C.S., F.R.C.P., Obstetric Physician, University College Hospital. Seventh Edition. 503 Engravings. 18s. net.

Manual of Midwifery. By T. W. Eden, M.D., C.M.Edin., F.R.C.P.Lond., Obstetric Physician and Lecturer on Practical Midwifery, Charing Cross Hospital. Third Edition. 339 Illustrations. 15s. net.

BY THE SAME AUTHOR.

Manual of Gynæcology. 272 Illustrations. 18*s*. net.

A Short Practice of Midwifery, embodying the Treatment adopted in the Rotunda Hospital, Dublin. By Henry Jellett, M.D., B.A.O.Dub., Master, Rotunda Hospital, Dublin. Sixth Edition. 4 Coloured Plates and 207 Illustrations. 10*s*. 6*d*. net.

BY THE SAME AUTHOR.

A Short Practice of Midwifery for Nurses, with a Glossary of Medical Terms, and the Regulations of the C.M.B. Third Edition. 4 Coloured Plates and 164 Illustrations. 6*s*. 6*d*. net.

ALSO

A Short Practice of Gynæcology. Third Edition. 310 Illustrations (some coloured). 12*s*. 6*d*. net.

A Manual for Midwives. By C. J. N. Longridge, M.D., M.R.C.P., F.R.C.S., Examiner Central Midwives' Board. 3 Plates and 47 Illustrations. 3*s*. 6*d*. net.

A Short Manual for Monthly Nurses. By Charles J. Cullingworth, M.D., F.R.C.P., Obstetric Physician to St. Thomas's Hospital. Sixth Edition. 1*s*. 6*d*. net.

A Clinical Manual of the Malformations and Congenital Diseases of the Fœtus. By Prof. Dr. R. Birnbaum. Translated and Annotated by G. Blacker, M.D., F.R.C.P., F.R.C.S., Obstetric Physician to University College Hospital. With 66 Illustrations. 15s. net.

A Text-Book of Embryology. By F. R. Bailey, A.M., M.D., Adjunct Professor of Histology and Embryology, Columbia University, and A. M. Miller, A.M., Instructor in Histology and Embryology. Second Edition. 515 Illustrations. 21s. net.

A Laboratory Text-Book of Embryology. By C. S. Minot, LL.D., D.Sc., Professor of Comparative Anatomy, Harvard Medical School. Second Edition. 262 Illustrations. 16s. net.

Outlines of Gynæcological Pathology and Morbid Anatomy. By C. Hubert Roberts, M.D.Lond., Physician to the Samaritan Free Hospital for Women. 151 Illustrations. 21s.

A Lecture on Dysmenorrhœa. By R. A. Gibbons, M.D., F.R.C.S.E., Physician to the Grosvenor Hospital for Women. 2s. net. **A Lecture on Sterility: its Ætiology and Treatment.** 2s. net. **A Lecture on Pruritus Vulvæ: its Ætiology and Treatment.** 2s. net.

Medical Jurisprudence Ophthalmology & Dermatology

Medical Jurisprudence: its Principles and Practice. By Alfred S. Taylor, M.D., F.R.C.P., F.R.S. Sixth Edition, by Fred. J. Smith, M.D., F.R.C.P., Physician to, and Lecturer on Forensic Medicine at, the London Hospital. 2 vols. 20 Engravings. 42*s.* net.

Lectures on Medical Jurisprudence and Toxicology. By Fred. J. Smith, M.D., F.R.C.P., F.R.C.S.Eng., Physician to, and Lecturer on Forensic Medicine and Toxicology at, the London Hospital. Second Edition. 8*s.* 6*d.* net.

BY THE SAME AUTHOR.

Law for Medical Men, containing Extracts from Acts of Parliament interesting to Medical Men. 10*s.* 6*d.* net.

Medical Ophthalmoscopy: A Manual and Atlas. Fourth Edition. By Sir W. R. Gowers, M.D., F.R.S., and Marcus Gunn, M.B., F.R.C.S., Surgeon to the Royal London Ophthalmic Hospital. Autotype Plates and Woodcuts. 14*s.* net.

Manual of Ophthalmic Surgery and Medicine. By W. H. H. Jessop, M.A., F.R.C.S., Senior Ophthalmic Surgeon to St. Bartholomew's Hospital. Second Edition. 8 Plates and 155 other Illustrations. 9*s.* 6*d.* net.

Refraction of the Eye: a Manual for Students. By Gustavus Hartridge, F.R.C.S., Consulting Surgeon to the Royal Westminster Ophthalmic Hospital. Fifteenth Edition. 107 Illustrations, also Test-types, etc. 5*s.* net. **The Ophthalmoscope: a Manual for Students.** Fifth Edition. 68 Illustrations and 4 Plates. 4*s.* net.

Diseases of the Eye: a Manual for Students and Practitioners. By J. Herbert Parsons, D.Sc., M.B., B.S., F.R.C.S., Ophthalmic Surgeon, University College Hospital; Surgeon, Royal London (Moorfields) Ophthalmic Hospital. Second Edition. 309 Illustrations and 17 Coloured Plates. 12*s.* 6*d.* net. **Elementary Ophthalmic Optics, including Ophthalmoscopy and Retinoscopy.** 66 Illustrations. 6*s.* 6*d.*

Sight Testing made Easy, including Chapter on Retinoscopy. By W. W. Hardwicke, M.D., M.R.C.P., Second Edition. 12 Engravings. 2*s.* 6*d.* net.

Royal London Ophthalmic Hospital Reports. By the Medical and Surgical Staff. Vol. XVIII, Part III. 5*s.* net.

Ophthalmological Society of the United Kingdom. Transactions. Vol. XXXII. 12*s.* 6*d.* net.

A Text-Book of Diseases of the Skin. By J. H. Sequeira, M.D., F.R.C.P., Physician to the Skin Department, London Hospital. With 44 Plates in Colours and 179 Text-figures. 25*s.* net.

The Diagnosis and Treatment of Syphilis. By Tom Robinson, M.D.St. And. Second Edition. 3*s.* 6*d.* **The Diagnosis and Treatment of Eczema.** Second Edition. 3*s.* 6*d.*

Otology ⸗ Pædiatrics ⸗ Dentistry

The Labyrinth of Animals, including Mammals, Birds, Reptiles, and Amphibians. By Albert A. Gray, M.D.(Glas.), F.R.S.E., Surgeon for Diseases of the Ear to the Victoria Infirmary, Glasgow. Vol. I, with 31 Stereoscopic Plates. 21s. net (including Stereoscope). Vol. II, with 45 Stereoscopic Plates, 25s. net.

Some Points in the Surgical Anatomy of the Temporal Bone from Birth to Adult Life. By Arthur H. Cheatle, F.R.C.S., Aural Surgeon to King's College Hospital. 112 Illustrations. 5s. net.

Diseases of the Ear, including the Anatomy and Physiology of the Organ, together with the Treatment of the Affections of the Nose and Pharynx. By T. Mark Hovell, Senior Aural Surgeon to the London Hospital. Second Edition. 128 Engravings. 21s.

The Diseases of Children. By Sir James F. Goodhart, Bart., M.D., F.R.C.P., and G. F. Still, M.D., F.R.C.P., Professor of the Diseases of Children, King's College. Ninth Edition. 34 Illustrations. 15s. net.

The Wasting Diseases of Infants and Children. By Eustace Smith, M.D., F.R.C.P. Sixth Edition. 6s.

On the Natural and Artificial Methods of Feeding Infants and Young Children. By Edmund Cautley, M.D., Physician to the Belgrave Hospital for Children. Second Edition. 7s. 6d.

An Introduction to Dental Anatomy and Physiology, Descriptive and Applied. By A. Hopewell-Smith, L.D.S.Eng., Lecturer on Dental Anatomy and Physiology, Royal Dental Hospital, London. With 6 Plates and 340 Illustrations. 18s. net.

Dental Anatomy, Human and Comparative: a Manual. By Charles S. Tomes, M.A., F.R.S. Sixth Edition. 286 Engravings. 12s. 6d. net.

BY THE SAME AUTHOR.

A System of Dental Surgery. By Sir John Tomes, F.R.S. Revised by C. S. Tomes, M.A., F.R.S., and Walter S. Nowell, M.A.Oxon. Fifth Edition. 318 Engravings. 15s. net.

Practical Treatise on Mechanical Dentistry. By Joseph Richardson, M.D., D.D.S. Seventh Edition, revised and edited by George W. Warren, D.D.S. 690 Engravings. 22s.

An Atlas of Dental Extractions, with Notes on the Causes and Relief of Dental Pain. By C. Edward Wallis, M.R.C.S., L.R.C.P., L.D.S., Assistant Dental Surgeon, King's College Hospital. With 11 Plates. 3s. 6d. net.

Decay in Teeth: an Investigation into its Cause and Prevention. By J. Sim Wallace, M.D., D.Sc., L.D.S.R.C.S. Second Edition. 5s.

A Manual of Dental Metallurgy. By Ernest A. Smith, Assay Office, Sheffield. Third Edition. 38 Illustrations. 6s. 6d. net.

Dental Materia Medica, Pharmacology, and Therapeutics. By Charles W. Glassington, M.R.C.S., L.D.S.Edin.; Senior Dental Surgeon, Westminster Hospital. Second Edition. 6s. net.

Tropical Diseases & Chemistry

The Malarial Fevers, Hæmoglobinuric Fever and Blood Protozoa of Man. By Charles F. Craig, M.D., Captain U.S. Army. With 4 Coloured Plates and numerous Drawings. 20*s.* net.

Waring's Bazaar Medicines of India. See page 6.

Prout's Elementary Hygiene. See page 4.

The Malarial Fevers of British Malaya. By Hamilton Wright, M.D. (McGill), Director of the Institute for Medical Research, Federated Malay States. Map and Charts. 3*s.* net. **The Etiology and Pathology of Beri-Beri.** With Map and Charts. 3*s.* net.

Report on the Prevention of Malaria in Mauritius. By Sir Ronald Ross, K.C.B., F.R.S. 25 Illustrations. 5*s.* net.

On the Causes and Continuance of Plague in Hong Kong. By W. J. Simpson, M.D., F.R.C.P. 10*s.* net. **Report on Plague in the Gold Coast in 1908.** Illustrated. 2*s.* net.

On the Outbreak of Yellow Fever in British Honduras in 1905. By Sir Rubert Boyce, M.B., F.R.S. 3*s.* 6*d.* net.

Treatise on General and Industrial Chemistry. By Dr. Ettore Molinari. Vol. I.—**Inorganic.** Translated by E. Feilmann, B.Sc., Ph.D., F.C.S. With 280 Illustrations and 3 Plates. 21*s.* net. Vol. II.—**Organic.** Translated by T. H. Pope, B.Sc., F.I.C. With 506 Illustrations. *In the Press.*

The Preparation of Organic Compounds. By E. de Barry Barnett, B.Sc. With 50 Illustrations. 8*s.* 6*d.* net.

Fatty Foods: their Practical Examination. By E. R. Bolton and C. Revis. With 7 Plates and 36 Text-figures. 10*s.* 6*d.* net.

The Plant Alkaloids. By T. A. Henry, D.Sc., Superintendent of Laboratories, Imperial Institute. 18*s.* net.

A History of Chemistry. By the late J. Campbell Brown. Edited by H. H. Brown. With 120 Illustrations. 10*s.* 6*d.* net.

Microbiology for Agricultural and Domestic Science Students. Edited by C. E. Marshall, Professor of Bacteriology Michigan Agricultural College. With 128 Illustrations. 10*s.* 6*d.* net.

Cocoa and Chocolate: their Chemistry and Manufacture. By R. Whymper. With 13 Plates and 19 Figures. 15*s.* net.

Annual Tables of Constants and Numerical Data. Chemical, Physical, and Technological. Volume I. Cloth, 24*s.* net.

Chemistry & Physics

The Chemical World. A Monthly Journal of Chemistry and Chemical Engineering. Edited by W. P. Dreaper, F.I.C., F.C.S., 6*d*. net. 6s. per annum post free, British Isles; 8s., Abroad.

The Analyst's Laboratory Companion. By A. E. Johnson, B.Sc., F.I.C. Fourth Edition. 6s. 6*d*. net.

Commercial Organic Analysis: a Treatise on the Properties, Modes of Assaying, Proximate Analytical Examination, etc., of Organic Chemicals and Products. By A. H. Allen, F.I.C. Fourth Edition, in 8 vols. Edited by W. A. Davis, B.Sc., A.C.G.I., Henry Leffmann, M.A., M.D., and S. S. Sadtler, S.B. Vols. 1, 2, 3, 4, 5, 6, and 7 ready. 21s. net. each. [Prospectus on application.]

Volumetric Analysis; or, the Quantitative Esti- mation of Chemical Substances by Measure. By Francis Sutton, F.C.S., F.I.C. Tenth Edition. 121 Engravings. 21s. net.

Volumetric Analysis for Students of Pharma- ceutical and General Chemistry. By C. H. Hampshire, B.Sc., A.I.C., Demonstrator in Chemistry, Pharmaceutical Society. 3s. 6*d*. net.

Notes on Chemical Research. By W. P. Dreaper, F.I.C., Editor of 'The Chemical World.' 2s. 6*d*. net.

The Physics and Chemistry of Colloids. By E. Hatschek. 14 Illustrations. 2s. 6*d*. net.

A Manual of Chemistry, Theoretical and Prac- tical. By Sir William A. Tilden, D.Sc., F.R.S. 143 Woodcuts. 10s.

Valentin's Practical Chemistry. By Dr. W. R. Hodgkinson, F.R.S.E. Tenth Edition. 97 Illustrations. 10s. net.

Qualitative Analysis and Practical Chemistry. By Frank Clowes, D.Sc.Lond., Emeritus Professor of Chemistry in the University Coll., Nottingham. Eighth Edition. 102 Engravings. 7s. 6*d*. net.

Quantitative Analysis. By Frank Clowes, D.Sc.Lond., and J. B. Coleman, A.R.C.Sci. Dub.; Professor of Chemistry, South-West London Polytechnic. Ninth Edition. 133 Engravings. 10s. 6*d*. net.

BY THE SAME AUTHORS.

Elementary Practical Chemistry.

Part I. Fifth Edition. General Chemistry. 75 Engravings. 2s. 6*d*. net.
Part II. Sixth Edition. Analytical Chemistry. 20 Engravings. 3s. 6*d*. net.

A Course of Practical Chemistry. By A. B. Ryley, M.A., Malvern College. Illustrated. Interleaved. 4s. 6*d*. net.

Introduction to Chemical Analysis. By Hugh C. H. Candy, B.A., B.Sc., F.I.C. 3s. 6*d*. net.

Researches on the Affinities of the Elements. By Geoffrey Martin, B.Sc Lond. Illustrated. 16s. net.

A Handbook of Physics and Chemistry for the Conjoint Board. By H. E. Corbin, B.Sc.Lond., and A. M. Stewart, B.Sc.Lond. Fourth Edition. 183 Illustrations. 7s. 6*d*. net.

A Treatise on Physics. By Andrew Gray, LL.D., F.R.S., Professor of Natural Philosophy in the University of Glasgow. Vol. I. Dynamics and Properties of Matter. 350 Illustrations. 15s.

Physics
Microscopy Miscellaneous

A Text-book of Physics. Edited by A. W. Duff, D.Sc., Second Edition. 525 Illustrations. 10*s.* 6*d.* net.

A Text-book of Physical Chemistry. By A. W. Ewell, Ph.D. 102 Illustrations. 9*s.* 6*d.* net.

The Conduction of Electricity through Gases and Radio-activity. By R. K. McClung, M.A., D.Sc., Lecturer in Physics, University of Manitoba. 78 Illustrations. 7*s.* 6*d.* net.

Physical Measurements. By A. Wilmer Duff, D.Sc., and A. W. Ewell, Ph.D. Second Edition. 78 Illustrations. 7*s.* 6*d.* net.

The Microscope and its Revelations. By the late William B. Carpenter, C.B., M.D., F.R.S. Eighth Edition, by the Rev. W. H. Dallinger, F.R.S. 23 Plates and 800 Wood Engravings. 28*s.*; or, in two vols., sold separately, cloth, 14*s.* each. Vol. I. The Microscope and its Accessories. Vol. II. The Microscope, its Revelations.

The Microtomist's Vade-Mecum. By Arthur Bolles Lee. Sixth Edition. 15*s.* net.

The Quarterly Journal of Microscopical Science. Edited by Sir E. Ray Lankester, K.C.B., M.A., D.Sc., LL.D., F.R.S. 10*s.* net.

Manual of Botany, in two Vols. By J. Reynolds Green, Sc.D., M.A., F.R.S. Vol. I. Morphology and Anatomy. Third Edition. 778 Engravings. 7*s.* 6*d.* Vol. II. Classification and Physiology. Second Edition. 466 Engravings. 10*s.* **An Introduction to Vegetable Physiology.** Third Edition. 182 Illustrations. 10*s.* 6*d.* net.

A Manual of Structural Botany. By H. H. Rusby, M.D., Professor of Materia Medica, Columbia University. With 599 Illustrations. 10*s.* 6*d.* net.

Plant Anatomy. By W. C. Stevens, Professor of Botany in the University of Kansas. Second Edition. 152 Illustrations. 10*s.* 6*d.* net.

The Tobacco Habit: its History and Pathology. By H. H. Tidswell, M.R.C.S., L.R.C.P. 3*s.* 6*d.* net.

The Principles of Aeroplane Construction. By Rankin Kennedy, C.E. 51 Illustrations. 5*s.* net.

Therapeutic Electricity and Practical Muscle Testing. By W. S. Hedley, M.D. 110 Illustrations. 8*s.* 6*d.*

A Manual for Hospital Nurses. By E. J. Domville, Surgeon, Devon and Exeter Hospital. Ninth Edition. 1*s.* 6*d.* net.

The Dawn of the Health Age. By Benjamin Moore, M.A., D.Sc., M.R.C.S., L.R.C.P. Cloth, 3*s.* 6*d.* net. Paper, 1*s.* net.

Nursing, General, Medical, and Surgical. By W. J. Hadley, M.D., Physician, London Hospital. Second Edition. 3*s.* 6*d.* net.

St. Thomas's Hospital Reports. Vol. 39. 8*s.* 6*d.* net.

Guy's Hospital Reports. Vol. 51. 10*s.* 6*d.* net.

Who's Who in Science. An International Biographical Directory of the World's Leading Scientists. Edited by H. H. Stephenson. 1913 Volume. 8*s.* net.

J. & A. CHURCHILL
LONDON: 7 GREAT MARLBOROUGH STREET