CAMPBELL ORATION

Delivered at Belfast on 19th January, 1933.

THE PROBLEM OF THE STREPTOCOCCUS

BY

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My first wish is to thank the Committee of the Robert Campbell Memorial Oration, in particular Sir Thomas Houston, for the very great honour they have conferred on me to-night. The magnitude of the distinction so towers over me that it exposes the futility of words to express how much I appreciate the honour.

To deliver an oration is an ordeal. It is accentuated by having to follow the footsteps of such masters of oratory as Colonel Sinclair, Sir Thomas Houston, Sir John Campbell, and Professor Fullerton.

In the last oration Professor Fullerton prophesied: "As the years roll on, the friends and associates of the late Robert Campbell will one by one follow him into the great unknown, and the orators of the next generation will know him only by name." The whirligig of time has spun faster than Professor Fullerton dreamt. It was never my privilege to know Robert Campbell or to come under his influence as a teacher. It is with diffidence, then, that I speak of one who was the friend, the colleague, or the teacher of many facing me.

My uncle, the late Dr. Boyd of Ballymoney, was proud to possess his friendship, and the sole contact I can claim was to stand with him among the trees of Templepatrick when the living memory became tradition. Previous orators have crystallized this tradition in words. They described his outstanding ability as a surgeon; his work in the Royal Victoria Hospital and the Queen Street Hospital for Sick Children; how in the latter he gave his energies to the love of children. He was among the pioneers of modern surgery in Belfast. As far back as 1910 he emphasized the fact that a distinction could be drawn between the types of appendicitis. His operative treatment of hernia in young infants was in advance of the times. He occupied the honoured position of president of the Ulster Medical Society and of the Belfast Branch of the British Medical Association.

His name is perpetuated not by a list of scientific abstracts or attachment to a particular operation, but rather, following the tradition of Graves and Stokes and other Irish physicians, hands down a reputation of penetrating clinical observation and sound judgment in diagnosis.

He was described as the perfect teacher, remembered by all whom he taught by the clarity with which he defined the essentials of a problem.

But from all the records and from all to whom I have gone for knowledge, the personality and character of the man was most remembered. I regret that I cannot speak except from hearsay, and realize how inadequate for the occasion are my remarks, but I understand that I am to be followed by those who were personal friends of Robert Campbell, and I must leave them to fill the gaps.

In choosing streptococci as a subject for this oration, I did so in trepidation when faced with the expanse of ground covered by the literature and the many windows through which the subject may be viewed. There is but one excuse to offer for my boldness—the privilege of working with Sir Thomas Houston in the laboratory of the Royal Victoria Hospital at one branch of the streptococcal problem.

To attempt to cover even a portion of streptococcal history, involving the questions of infection and immunity, clinical and pathological investigations, and the study of the organism from the bacteriological aspect, would be a task equally beyond my power and the scope of this address. I must escape, therefore, into the general and leave the particular, conscious the while of skimming over many points of hot debate and guilty of statements that leave me open to rebuke.

Among the many organisms associated with pathological conditions in man the position of the streptococcus is unique. Its methods of attack are bewildering in their complexity; it is sometimes obvious, at other times refusing to yield its secrets under cross-examination of the third degree. It may be a harmless saprophyte. It may strike with terrible force. Few indeed are the diseases known to man which have not, at some time or other, been attributed to the streptococcus; yet comparatively few in which positive relationship has been definitely established. As a cause of inflammation and suppuration its position is undisputed. No tissue or organ escapes. Its ravages vary from trivial localized inflammations to rapidly spreading infections—all too frequently ending in fatal septicæmia. It is the bane of the surgeon and midwife. Erysipelas and puerperal fever are included in the list, and the association of its name with rheumatism, in particular the acute form, brings within its province the far-reaching effects of heart disease. Streptococci invade the lymphatic defences, the mucous and the serous membranes of the body—tonsillitis, peritonitis, cholecystitis, otitis, meningitis—the roll goes on. They are the most frequent and serious offenders in the secondary infections, those following measles, whooping-cough, influenza, and a list of other primary infections. In few of these random clinical entities can it be claimed that streptococci are specific. Other organisms may simulate the picture. The clinical description rests on an anatomical basis. The bacteriological diagnosis will depend on the isolation of the organism.

In order to prove that a clinical picture is caused by a particular coccus or bacillus—to prove its specificity—certain conditions must be fulfilled. These were laid down in the early days of the science by Robert Koch, and, with slight modifications, the outcome of modern research, are still the golden rules of bacteriology.

As enunciated by Topley and Wilson, they are as follows :—

(1) The organism should be found in all cases of the disease in question, and its distribution in the body should be in accordance with the lesions observed.

(2) The organism must be shown to be a living thing, and must be cultivated outside the body of the original host, in pure culture, for several generations.

(3) The organism, so isolated, must reproduce the disease in other susceptible animals.

To make streptococci found in connection with human disease conform to Koch's postulates as proof of specific relationship, constitutes the problem of the streptococcus. The nature of the organism has been to evade the limitations imposed.

The first postulate necessitates the recognition and definition of character that will separate individual species. In some this can be done with moderate certainty and ease. The tubercle bacillus is an example. But when streptococci are considered the state of affairs is far from simple. So difficult, in fact, has it proved, that the greater part of the work on streptococci has developed along the lines of academic research, the biological or 'botanical' study of the organism divorced from its clinical pabulum.

Within recent years the elucidation of many bacteriological problems has served to orientate afresh the views of streptococcal infections. There is still much to be solved in the laboratory before the application of this knowledge to clinical medicine can be realized.

From the bacteriological standpoint it has been well said: "The story of the streptococci is the history of their classification." So, to pave the way for topics of more general interest, it is essential to review some of the steps in this history.

In 1874, Billroth, describing the appearance of certain microbes, gave the name 'streptococcus' to a type of cocci which characteristically grew in chains. This broad distinction, this picture of a series of cocci in the form of a chain, is the primary distinctive feature of the group. The description is morphological.

The first relationship was to erysipelas. To similar organisms, isolated from purulent discharges, Rosenbach added the term 'pyogenes.' It was soon shown that the erysipelas strains could reproduce the reactions of streptococcus pyogenes.

Attention was directed to the physical characteristics and physiological properties of organisms. This involved the study of the appearances of colonies on solid media and nature of growth in fluid; pigment formation; respiration and the oxygen requirements; nutrition and the utilization of carbohydrates and protein; enzyme production; and other metabolic processes. All these, by using suitable media and technique, came to be used as differentiating tests and criteria by which bacteria could be separated.

A distinctive test to prove of great importance in classification was shown by Schotmuller to be the action of streptococci on red blood-cells. It was found that

certain streptococci, when grown on a solid medium containing blood, had the power of hæmolysing the red cells. These are hæmolytic streptococci. They are recognized by the appearance of a colourless transparent halo on the blood-agar around the colony. A second group produce a green ring. This is the streptococci viridans. A third has no effect on blood. The ability to ferment certain carbohydrates, evidenced by the production of acid in fluid media containing various sugars, provided a further means of differentiation. Schemes of classification were devised by grouping together streptococci with biological properties in common. A multiplicity of tests were added, further subdividing the groups. Classification became more kaleidoscopic with each new method of technical discrimination. On this principle streptococci have been divided into an ever increasing number of individual species, which appear to make it impossible to link a classification on rigid biological standards to the pathological conditions from which the streptococci have been obtained. The central characters with broad outlines remained of value in classification, but the margins fused into neighbouring groups. Thus the division into hæmolytic and non-hæmolytic is of practical importance. From the latter the pneumococcal and the enterococcal groups can be separated out.

Serological methods of dividing and grouping organisms by agglutination and complement fixation have proved invaluable in classifying certain other bacterial species. With the exception of the pneumococcus, they have as yet failed with streptococci to fix clearly defined landmarks.

Sir Frederick Andrewes, in a recent medical research council report, summed up the results of seven years work on the serological study of two hundred strains of hæmolytic streptococci. These included strains from erysipelas, puerperal fever, scarlet fever, and pyogenic infections. He concludes: "The more one studies hæmolytic streptococci, the more strongly is the impression gained that they are in a constant state of flux, in which it is difficult to find any firm foundation for a permanent systematic classification; . . . only exceptionally are two streptococci serologically identical and very rarely are they entirely dissimilar."

It can be understood, then, how difficult it would be to apply Koch's first postulate if the strict letter of the law be adhered to in relation to biological classification.

The influence of Koch was to establish the principle of fixity in bacterial species, but within recent years a mass of literature, founded on experimental research on many types of organism, has gone far to show that much believed to be fixed can be altered, and that the permanence of many standards must be accepted as relative and not incapable of change. Most of the work is of academic interest, but the theory of bacterial variation has influenced the growth of modern conceptions of infection.

The history of the subject is long. I can merely indicate a few points of immediate interest. Before touching on streptococci it is necessary to turn to the investigation of another group—the typhoid. Arkwright, studying the appearance of colonies of the typhoid bacillus, discovered that atypical colony forms could be obtained by

planting out old broth cultures. These he called 'rough' in distinction to the 'smooth'—the original type of colony.

The change went deeper. Many characters of the 'smooth' were altered in the 'rough.' They might have been classed as different species, yet the one evolved from the other. The most important, from the practical point of view, concerned pathogenicity. The 'rough' variants were non-pathogenic. An experiment outside the body had demonstrated a changed relationship of the bacillus to disease.

With streptococci variations have also been produced. Cowan developed avirulent colonies of streptococci from a virulent stock. It is claimed that hæmolytic streptococci can be changed to non-hæmolytic, strepococci to pneumococci. A host of other alterations in character are described. Most light has been thrown on pneumococci. Griffiths, by growing pneumococci in immune serum—the serum of a rabbit immunized to a similar type of pneumococcus—produced 'rough' variants, which had lost their specific type, that is, could not be identified as type I or II or III pneumococcus. (Julianelle obtained similar results with Friedlander's bacillus.) The 'rough' change was associated with loss of capsule and loss of virulence. Knowledge of the biochemical structure of organisms has advanced within the last decade, chiefly through the work of Heidelberger, Avery, and their co-workers. From the pneumococcus they were able to isolate protein fractions and a polysaccharide element. This last was present in the smooth, capsulated, virulent pneumococcus, but could not be discovered in the 'rough' avirulent variant. In the pneumococcus, then, virulence depends on the linkage of a specific carbohydrate to the bacterial protein. This carbohydrate is associated with the capsule of the pneumococcus. Other members of the streptococcal group have been investigated on these lines, and Dr. Haslett, working in the Royal Victoria Hospital, has succeeded in isolating the carbohydrate and protein components of the enterococcus.

Most of the changes in behaviour have been achieved by growing the organism in an environment which accentuated its struggle for existence. Laboratory methods can, at the best, be but crude reproductions of the conditions in the complex laboratory of the human body. The probability of similar alterations in virulence occurring in the latter is feasible, and may account in part for decline in infection. The possibility, on the other hand, of the reverse change, that of avirulence to virulence, must be considered. Experimental proof is scanty. Griffith succeeded in changing an avirulent pneumococcus to the virulent form. Speculation would lead to questions of the rise of epidemics from the acquisition of pathogenicity by a previously harmless organism.

The Role of the Streptococcus in Disease.

The property of hæmolysing blood is in general terms a vertical partition separating the sheep from the goats—the pathogenic streptococcus from the non-pathogenic.

The hæmolytic are associated with acute infections. Their presence is characterized by their tendency to spread into surrounding tissues and cause a diffuse

inflammatory reaction; to enter lymphatics and give rise to lymphangitis; and their ability to invade the blood-stream and generate septicæmia. In possession of these powers the hæmolytic streptococcus becomes a dangerous enemy. During the war the infection of wounds delayed healing, increased the disabilities, and added to the death-roll. Bacteriological examination proved the hæmolytic streptococcus the most serious offender.

I propose to pass on to certain clinical conditions in which the hæmolytic streptococcus has specific rights. Three diseases are prominent. They are scarlet fever, erysipelas, and puerperal fever.

Scarlet Fever.

The presence of hæmolytic streptococci in throats of scarlet fever patients is an old observation. Bliss showed that the organism was present in the acute stage and generally disappeared from the tonsil at the end of the illness. For some time, however, definite evidence was not obtained to prove the essential role of the hæmolytic streptococcus. The strains isolated were indistinguishable from those derived from other sources. Animal experiments failed to reproduce a syndrome comparabe to scarlet fever. The concensus of opinion regarded hæmolytic streptococci as of secondary rather than primary importance in scarlet fever. The typical rash was thought to be toxic in origin. Schultz and Charlton showed that the sera of convalescent patients, and some normal sera, injected intradermally, caused a blanching of the rash at the site of injection. The Schultz-Charlton reaction led to the assumption that serum of convalescence contained an anti-toxin able to neutralize the toxin producing the rash.

In 1923, the Dicks published their studies on the ætiology of scarlet fever. Their work is a landmark in streptococcal literature. From the septic finger of a nurse who was suffering from scarlet fever, they isolated a hæmolytic streptococcus. The throats of five healthy volunteers were swabbed with a culture of this organism. Of the five, one passed through an attack of scarlet fever, one developed acute sore throat without signs of a rash, and the rest suffered no ill effects. At the same time a second series of volunteers were swabbed with a sterile filtrate of the culture. These did not react. The hæmolytic streptococcus had produced the scarlet fever syndrome in a human subject, and it was inferred that the coccus itself was responsible, since the filtrate was innocuous on the throat. The rash and toxæmic symptoms of scarlatina were attributed to a toxin circulating in the blood-stream from the focus in the throat. A difficulty arose. The toxin could not be demonstrated. Rabbits were injected, but failed to provide a clue. It was not until the Dicks again turned to man as a test animal that success was gained. They filtered cultures of scarlet fever hæmolytic streptococci. The filtrates were diluted. A small quantity injected intradermally was followed by an erythematous reaction in a proportion of human subjects who had not had scarlet fever. Round the site of injection the skin became red, raised, and painful. The reaction appeared within six to twelve hours, reached a maximum at or about twenty-four hours,

and then gradually faded. This positive response denotes susceptibility to scarlet fever. It marks an absence of antitoxin in the individual. A negative test indicates the presence of antitoxin and resistance to scarlet fever. The test, which has been widely applied, is known as the Dick test. Positive results are obtained in about eighty-five per cent. of patients during the first week of scarlet fever. The test is negative at convalescence.

With the discovery of a toxin and evidence of an antitoxin in the sera of those not susceptible, the next step would be to procure antitoxin for prophylaxis and treatment. Antitoxic sera were prepared, but the standardization of such sera introduced a problem, as no laboratory animal was susceptible to the toxin. The toxin-antitoxin technique, used in the standardization of anti-diphtheritic serum, was therefore unavailable. Man alone was susceptible, and the toxin-antitoxin method of standardization is carried out by skin tests on susceptible men.

The treatment of scarlet fever by serum has been widely practised. Considerable data of the results have been published. It would appear that anti-scarlatina serum, if given early, checks the toxæmia caused by the circulating toxin, and is therefore of immediate benefit. It is doubtful if the complications of the disease can be mitigated. The serum neutralizes the toxin of the hæmolytic streptococcus, but seems to have little influence on the localized throat condition or its sequelæ—otitis media and mastoid disease. The organism is not necessarily destroyed, and a source for infective spread will remain.

Erysipelas.

Erysipelas is an acute infection of the skin by a hæmolytic streptococcus.

Fehleisen, in 1883, isolated the streptococcus from the lesion, and reproduced a similar picture in man and animals by the injection of pure cultures. The penetrating power of the streptococcus is seen in the fiery spread of inflammation. The lymphatics are infiltrated, and ensuing œdema gives a raised margin. From this margin the organism can be most readily obtained by skin puncture or by injecting sterile saline into the skin and aspirating the fluid.

Infection occurs through a break in the skin. The facial, the common type, may originate from the nasal passages. It may arise as a complication of other streptococcal infections, for example, a septic wound. One attack will not guarantee immunity. Certain persons, on the contrary, are liable to repeated attacks of erysipelas. Direct transportation by hand of surgeon, nurse, or dresser was responsible for the spread of the disease in the pre-Listerian era, when erysipelas was rampant in institutions. The association with puerperal fever was recognized in those days; and now bacteriology unites the associates by incriminating the hæmolytic streptococcus as the most frequent and deadly cause of puerperal infection.

Puerperal Fever.

The crusade of Semmelweis in the wards of Vienna was the effort of a man convinced that childbirth fever was an infectious disease, carried from case to case, and that the scourge could be checked. Proof of his theory came with the advance of antisepsis and asepsis. Puerperal fever is, in most cases, an infection with hæmolytic streptococci.

But how does infection occur? Is it of exogenous origin, or is it due to an organism, present before labour, asserting itself at the puerperium?

The 'normal' flora of the vagina is mixed. Streptococci are present in a high proportion of cases examined before and after delivery. Although non-hæmolytic varieties predominate, hæmolytic strains have been isolated, but the subsequent histories in these cases were for the most part uneventful. Puerperal fever may occasionally be an autogenous infection; the vast majority of cases arise from the introduction of a hæmolytic streptococcus at some time and by some means during labour.

Previous contact of the midwife with a septic case is the usual mode. The infection, however, may emanate from the throat of an attendant who is harbouring a virulent streptococcus, either accompanied with sore throat or as a carrier. The surgical mask forms a barrier to this potential source of infection.

The infectious nature of hæmolytic streptococcal disease is apparent. Modern knowledge of the more obvious manifestations has controlled many of the depredations. Other ways of spreading disease are less on the surface, and more often than not elude detection. One subtile means, by which the hæmolytic streptococcus preserves a grip on the community, lies in the prevalence of acute sore throat. In isolated case and epidemic form, the hæmolytic streptococcus is the usual infecting agent. Epidemics arise by passage of a virulent strain from one person to another. It is recognized that contaminated milk, traced to hæmolytic streptococcal mastitis in a cow, can be the source of propagation. Certain apparently healthy persons carry the hæmolytic streptococcus in the throat, and it has been shown that the carrier rate rises during an epidemic.

Glover and Griffith made an inquiry into outbreaks of acute tonsilitis in public schools. They traced the subsequent sequelæ, and in their report brought out many suggestive points. To quote from their summary: "Infection of the throat with hæmolytic streptococci produces varying clinical symptoms in different persons. These include—first, a symptomless infection or healthy carrier state; secondly, tonsillitis; thirdly, febricula, feverish catarrh or pharyngitis, without noticeable sore throat; fourthly, scarlet fever. Any of the three latter conditions may be followed by otitis media or acute rheumatism. . . . In any epidemic of scarlet fever, cases of tonsillitis and mild pharyngitis occur side by side with the cases of scarlet fever, and, if bacteriological examination be made, numbers of healthy carriers will be detected, all yielding the same type of hæmolytic streptococcus as the scarlatinal cases. These unsuspected sources of infection constitute one of the

most difficult problems in the control of scarlet fever." They add that overcrowding, bad ventilation, and deficient nutrition favour the spread of infection.

Here, then, are the clinical conditions of scarlet fever, erysipelas, puerperal fever, and acute tonsillitis, all due to streptococcus hæmolyticus. Possession of specific properties by the particular cocci identified with each disease would afford an explanation of the diversity of clinical picture. Some hold to this explanation, but the view at the moment is that the strains cannot be satisfactorily differentiated. Okell, in the Milroy lectures of the past year, expounds the 'unitarian' doctrine of hæmolytic streptococcal infection.

The gist of the theory briefly is :

The offensive weapons of the streptococcus are three in number. First is the pyogenic faculty, which causes an inflammatory reaction, with or without abscess formation; second, the power of invading the blood-stream; third, the ability to produce an exotoxin.

The first two are common property of all hæmolytic streptococci. The force behind these weapons will vary. They are direct-action tactics. The third is the long-range artillery by which the streptococcus entrenched in the tonsils or elsewhere bombards the organs and tissues by discharging a toxin into the circulation. This last form of attack is used specially by the scarlet fever strains, and for some time it was believed that the toxin was peculiar to these strains. Some yet say that it is. The unitarians, on the other hand, hold that all hæmolytic streptococci produce the same toxin. The differences are quantitative rather than qualitative, and a single antitoxin will neutralize toxin from any strain; the scarlatinal happen to yield a greater amount. The well-known surgical scarlet fever is cited as an example of the effect of the rash-producing toxin.

Each individual host will set up defences against these three weapons of the hæmolytic streptococcus. The resistance to pyogenicity and invasiveness has been difficult to assess. Yet in the reaction to the direct forces of a virulent streptococcus there are undoubted variations. The infective process may be trivial in one and intense in another.

More is known of the toxigenic property. The Dick test is a guide in separating the susceptible from the resistant, thus demonstrating the variability in effect of the toxin. So if hæmolytic streptococci differ in their powers of attack and meet a varying defence, the possibilities of variation in the type of lesion, in clinical syndrome, and in the grade of infection will be difficult to foretell. In summing up the arguments supporting the unitarian conception, Okell states : "It is as impossible to separate the several clinical and epidemiological forms of streptococcal disease as it is to distinguish specifically the streptococci found in connection with them. . . . It (the unitarian view) is in consonance with the curious sequences of propagation which may be observed in streptococcal diseases. It does some-

thing to explain the mysterious birth of streptococcal epidemics and the failure of hospital and other forms of isolation to control the incidence of scarlet fever." The outcome of practical interest has been the preference of anti-scarlatinal serum in treatment of all hæmolytic streptococcal infections.

To return once more to the division of streptococci into hæmolytic and non-hæmolytic. Having dealt briefly with the former, a few remarks on the latter are necessary to complete this sketch of streptococcal problems.

If the study of the first is fraught with pitfalls, that of the second is even more difficult. The role of hæmolytic streptococci in disease is certain, the details only being confused. With the non-hæmolytic the main issues are ill-defined. Most, if not all, of the types and variants—and they are numerous—are to be found unassociated with disease as saprophytes of the mucous membranes of the body. Proof of their infectivity is rendered difficult. They generally produce an inflammatory reaction less acute than that of the hæmolytic type. Virulence is low-grade. This apparent innocence is deceptive when it is realized that acute rheumatism and its sequelæ are ascribed to their influence.

The syndrome of rheumatic fever suggests a microbic origin. What the organism is, where it acts, and how it exercises its power, are problems that have faced all workers on the subject, which is one of the most perplexing and elusive of bacteriological studies. From the first a streptococcus has been suspect. The pioneer work of Poynton and Paine led research to the likelihood of a streptococcal origin of rheumatism. From the blood and joints of patients, and from tissues at post-mortem, they obtained an organism diplococcal in form. Rabbits injected intravenously with cultures developed arthritis and endocarditis. They believed the organism was the cause of rheumatism, and named it streptococcus rheumaticus. Other investigations and papers followed, notably the work of Beattie and his associates, who isolated diplococci from joints and tissues, using frequently post-mortem material. Their animal experiments supported the rheumatic association. A lack of conformity was evident, however, in the strains isolated. In many instances the biological characters were not defined, since the modern methods of differentiation were unknown. They mostly fell into the non-hæmolytic group, and could not be distinguished from the types found in mouth and intestine.

It so happened that the basis of much of the earlier work was founded on streptococci isolated usually from the dead, only infrequently from the living. Proof of association with rheumatism was sought chiefly in experiments on the rabbit. The fallacy of relying implicity on rabbit pathology was pointed out by Topley and Weir, who showed that a variety of streptococci from various sources unconnected with rheumatism could produce lesions similar to those of "rheumatic" strains.

In the search for an organism, cultures of joint fluids have, in the majority, proved sterile. Positive findings are recorded with sufficient irregularity to be exceptions. Swift and Kinsella, indeed, report eighty-five consecutive examinations

to be negative. The inability to grow out a streptococcus may, of course, be due in some measure to technique. Some streptococci are notoriously difficult to cultivate.

The results of blood-culture in acute rheumatism are also inconsistent. Herry records positive streptococcal cultures in forty-eight out of sixty cases, while Wright in four years' experience, using modern technique, failed to isolate an organism of any kind. Between these extremes the literature of positive results varies. The strains of streptococci that have been isolated were usually viridans in type.

It is difficult, then, to accept the conception of rheumatism as a blood infection; and that local lesions are due to proliferation of streptococci. Those who hold this view reply that cocci are only occasionally present in the blood-stream and joint fluid, where they are rapidly killed, and that they are to be found in tissues such as synovial membrane.

A relationship between tonsil infection and acute rheumatism has long been recognised. Diverse opinions are expressed on the role played by focal infection in the disease. The recent discussion before the Ulster Medical Society on tonsil infection produced many conflicting views.

The bacteriology of the tonsil is equally confusing. Mention has been made of the acute tonsillar inflammation of the hæmolytic streptococcus. The position with regard to the other types appears hopeless, particularly as a "normal" flora cannot be defined. Divers streptococci are found in health and disease, and assessment of predominance of type is open to criticism, so much depending on the cultural method employed. Certain media encourage some organisms and may inhibit others. The important organism may be missed. There is no reliable method of gauging the importance of those found. The disadvantages of surface swabbing can be partially overcome by tonsil puncture. This may single out a pure culture from a welter of types.

At the outset the bacteriological study of focal infection bristles with difficulties. Let us suppose that the rheumatic state is caused by a streptococcus abiding in the tonsil and circulating a toxin, then it becomes necessary to find a streptococcus with this specific property and show that its presence in the rheumatic is more consistent than in the normal subject. Recently two American workers vouch for such a specific coccus.

Birkhaug isolated a streptococcus from throats in acute rheumatic fever. It had no effect on blood-agar, and could be differentiated by fermentation and serological properties. He states that a toxin is produced which will give positive skin tests in rheumatic patients. To prove his contention, Birkhaug had the courage to inject the toxin into his wrist joint. He developed a febrile attack, which he describes was typical of rheumatic fever and yielded to salicylates.

A somewhat similar streptococcus has been described by Small. Their results await confirmation.

An alternative hypothesis is that of Zinsner and Yu, Swift, and others. Streptococci in the tonsil or some other focus, they argue, induce a state of general hypersensitivity of the tissues to bacterial products which in themselves are not necessarily toxic. The streptococcus concerned need not be a specific strain alone responsible for rheumatic fever, but the ability to produce the rheumatic manifestations may be shared by a variety of streptococci. A non-specific streptococcal factor evokes a state of allergy. This theory of the streptococcal rôle in rheumatism would rationalize the differences in streptococci classed as specific in the disease. It would also account for the variance in the interpretations of skin tests as an indication of specific infection.

Within the last few years hæmolytic streptococci have been added to the lists of suspects by Coburn in America, in this country by Schlesinger, Sheldon, Collis, and others. The latter noted that an outbreak of hæmolytic streptococcal sore throat among children in a rheumatic clinic was the precursor to a recrudescence of rheumatic signs and symptoms. A period elapsed from the onset of tonsillitis to the flaring-up of heart and joint symptoms. They suggest that initial infection in the throat may be overlooked in cases of acute rheumatism. I have quoted Glover and Griffith's observation of the rheumatic sequel to acute tonsillitis.

Rheumatic fever is an infection—a crime against mankind, a crime of breaking and entering. In the dock stands the streptococcus. The evidence against it is strong. As yet, the jury cannot agree, but the accused must not be discharged as not guilty; rather must we follow the old Scottish custom, and record our finding as "Not proven."

There is one condition in which a non-hæmolytic streptococcus is definitely responsible—subacute bacterial endocarditis.

The association of pyrexia, valvular disease, and the occurrence of emboli, combined with the lack of response to treatment, constitute a definite syndrome. The pathology is established. In 1903, Schotmuller isolated a streptococcus viridans from the blood of patients. All subsequent work has confirmed this finding. The strains isolated differ and they are normally the saprophytes of the body. It is of interest to note that a streptococcus, isolated from cases of endocarditis by Braxton Hicks (streptococcus zymogenes) is an enterococcus with the power of liquefying gelatin. Sir Thomas Houston has stressed the importance of this organism in rheumatic conditions.

The pathogenesis of subacute bacterial endocarditis is obscured as to why the valves of the heart are seized on by these low-grade organisms. According to some authorities, a chronic rheumatic lesion or a congenital defect are predisposing factors.

A focus situated in the valves ensures entry of streptococci to the blood-stream. Positive blood-cultures can generally be obtained. Wright reviews the literature of the disease and discusses the discrepancies in blood-culture results. He recommends the addition of sodium citrate to the medium and the taking of 20 c.c. of blood, to achieve success.

CHRONIC RHEUMATISM.

The bacteriology of chronic rheumatism probes chiefly into the question of focal infection. The medley of clinical conditions from vague 'rheumatic' pains to articular arthritis are collected under one name.

Sir Thomas Houston has been carrying out investigations in the study of the enterococcus in relation to chronic rheumatism. He has placed before the Ulster Medical Society the results of his work. His views on the subject, drawn from a vast experience in the diagnosis and treatment of these conditions, are so widely known in his own school that it would be an impertinence for me to attempt to review them in detail. He has drawn attention to the close connection between bowel disturbances and chronic rheumatism; to the fact that many diplococci described in the past as "rheumaticus" have been enterococci. If the test of heat resistance, his original observation, be taken as a criterion, many more might fall into this group. He has shown that enterococci are frequently found in the infective foci of tonsils, apical abscesses, and other lesions of patients suffering from one of the rheumatic states, and, as further proof, that the sera of many of these patients agglutinate the enterococcus.

These remarks of mine, I fear, have borne the stamp of haphazard sequence and confusion. In this respect, if no other, they are descriptive of the streptococcal problem. Topley and Wilson define infection as "any association of a parasite and host in which the reaction between them involved any damage, however slight, to the host's tissues."

The balance of power is an armed neutrality. The cells of the host and the cell of the parasite each have a complex struggle for existence. The barrier may be broken by a chink in the armour of the host, or by exaltation of the attacking forces of the parasite. The former represents a lowered resistance. It may occur through the breaking of hygienic laws, climatic conditions, unsuitable diet, vitamin deficiency, glandular disturbance—in other words any of the factors which disturb the normal functions of a particular organ or the body as a whole. And when none of these can be blamed, the responsibility can be placed on the shoulders of those ancient stalwarts—"the unknown factor" and "diathesis."

With a lowered resistance established, an organism, primarily present or entering from without, will find the scales loaded in its favour, and infection results. The first coincidence would be autogenous, the second exogenous infection.

From the other angle, experiments indicate, and the course of infection and epidemics suggest, that organisms pass through phases of virulence. The increase of virulence, for reasons unknown, may suffice to alter the reaction with the host, and the damage is done.

The streptococcal problem began with the recognition of cocci in chain formation. It has led far afield. It has strayed from the test-tubes of the clinical laboratory into the precincts of the biochemist and physicist. The aid of the statistician, epidemiologist, and other specialists has been enlisted. The ultimate goal of all lies in its application to clinical medicine.

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