T H E S I S

FOR THE DEGREE OF M.D. EDINBURGH UNIVERSITY

O B S E R V A T I O N S

ON A CASE OF ACUTE RHEUMATISM OF UNUSUAL SEVERITY WITH SPECIAL REFERENCE TO THE BACTERIOLOGY

by

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There has been for many years amongst both Clinicians and Bacteriologists a marked difference of opinion as to the causal agent of Acute Rheumatism and its allied conditions.

For centuries the origin of this disease accepted by most medical authorities, including the old authors of medical text-books, was to be found in the presence of some irritating chemical compound, such as uric or lactic acid, in the blood. This, they declared, was due to some flaw in the metabolic processes of the body which was in their opinion clearly demonstrated by the presence of calcareous deposits in the joint-cartilages and elsewhere. As time went on, however, and the causal relationship of micro-organisms to many of the infectious fevers and to disease in general came to be more widely recognised, doubts began to be cast on the accuracy of the old theory. Men began to consider the possibility of an organismal cause in this as well as in the other fevers, and efforts were made to isolate the specific/

specific germ.

In the year 1897, Achalme recorded that he had succeeded in isolating a gram-positive bacillus from several cases of acute Rheumatism. This was, however, found to be identical with Bacillus Welchii, and was considered to be merely a terminal infection, and not the true cause of the disease. A year or two after (1898-99), three Continental investigators, Triboulet, Westphal and Wassermann, observed and recorded several cases of Acute Rheumatism in which they had been able to isolate a small coccus. This discovery was verified by Poynton and Paine in this country, in 1899, and the morphological and cultural characters were worked out by them. They announced it to be of the nature of a diplococcus or short chained streptococcus, and to have very definite and distinguishing characteristics. It was called the Diplococcus Rheumaticus, and was found to be present both in the blood and in the diseased tissues of acute cases. Other investigators soon entered the field and took up the study of the organism, amongst whom, with others, were Beattie, Cole and Andrewes and Horder. The first mentioned published a review of experimental work done by himself on the "Relationship of the Micrococcus Rheumaticus to the Streptococcus pyogenes", in January, 1906. Cole had already published/

published some results of his work on the subject in 1904, and Andrewes and Horder made further reference to it in their article upon"Streptococci Pathogenic to Man", published in "The Lancet", 1906.

Since then much has been and is still being done in Britain, America and on the Continent to further elucidate the subject, but up till the present the results obtained have not been quite convincing, and the evidence brought forward to back up the various theories promulgated by well-known men is not a little confusing.

There can be no doubt, however, that the disease is infectious in nature, and is due to the action of a specific germ. What the exact nature of that germ is, time will reveal.

The case about to be described, and which constitutes the subject of this Thesis, goes to prove the above, and at the same time introduces a fresh element, namely, that of mixed infection.

During the past eighteen months many cases of Rheumatism, both acute and chronic, have passed through my hands. One of these stands out prominently from all the others, as showing how acute can be the infection, and to what a remarkable extent the various tissues of the body can be damaged. At the same/

same time it is a splendid example of how easily one may get mixed infection in this disease, and how difficult it is to explain the presence of other than the specific microbe in the blood and other tissues affected.

The following is a complete clinical description of the case referred to.

M.B., a girl aged twelve years, was admitted to the wards of St. Pancras Infirmary on November 27th, 1911, with the history that a day or two previous to admission she had got her clothes wet whilst out walking, and in consequence of this had caught a chill. On the evening of the 25th, she was taken suddenly with a violent pain in the right side of her chest. She went to bed, and remained there during the following day. A short, painful cough developed, and she began to complain of pains all over her body. On the morning of the 27th, her condition was so much worse that it was thought advisable to have her removed immediately to hospital.

When seen soon after admission, she was lying in bed on her right side, and her appearance gave one the impression that she was very ill. The only complaint she made was of pain in the right side of her chest, especially when she coughed or took/

took a deep inspiration. Her temperature was raised to 102° F., her pulse was rapid, 128 per minute, and her respirations were accelerated, 44 per minute. She had a short, hard, persistent cough, which evidently added to her distress. There was little or no expectoration. Cyanosis was absent, and though her breathing was quick it was not laboured. The pulse was of the usual fever type, and at that time was quite regular in rhythm and showed no signs of cardiac trouble.

The heart itself was apparently healthy, there being no appreciable enlargement of the organ, and no alteration in the sounds. Its action was rapid but regular, and the apex beat appeared in the normal position.

The lungs both showed signs of disease - the right marked, the left only slight. In the right, the lower lobe was consolidated and evidently pneumonic. Its movement was restricted, and on auscultating over it one heard typical tubular breathing, with accompanying fine crepitations and increased vocal resonance. The left lung, on the other hand, showed no definite signs of disease and, save for a small area of consolidation at the level of and internal to the inferior angle of the scapula, was apparently/

apparently healthy.

The joints were not affected, and could be moved freely without causing pain.

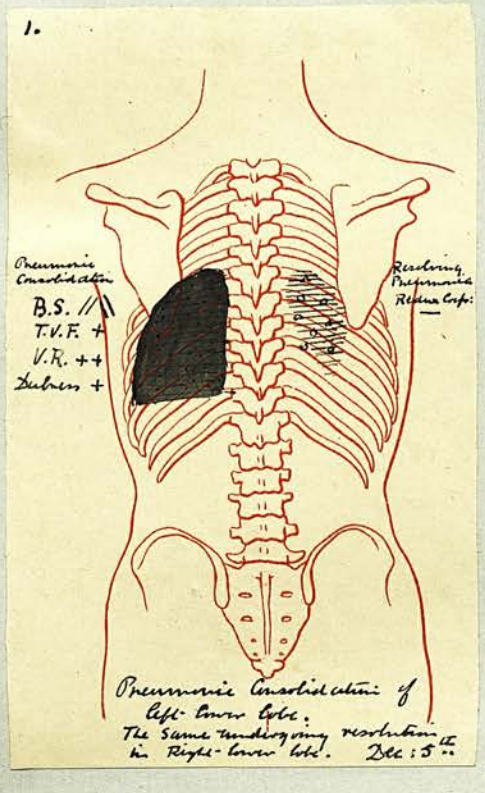
The tonsils were slightly enlarged, but there was no tonsilitis and no injection of the fauces. She was able to swallow quite well, and did not complain of sore throat.

She continued in this condition, without any noteworthy change either for better or for worse, until December 1st, when she began for the first time to complain of pains in her right knee joint. It was examined and found to be distinctly swollen, tender to touch and very painful when moved. There was fluid in the joint cavity, as was proved by the presence of fluctuation. On December 2nd, the left knee became similarly affected. The temperature rose to 103·4° F., the pulse became quicker in proportion, but retained its regularity, and the child began to look anxious.

The pain, which had practically disappeared from the right side of the chest, now appeared in the left, and the breathing in consequence became quicker and more distressed. The cough became more persistent and painful, though the expectoration

continued/

continued scanty. What she did cough up was blood-stained and viscid. The description of its microscopical appearance is given below.



An examination was made of the left side of the chest, and it was found that the lower lobe of the left lung had also undergone consolidation and had all the physical signs characteristic of Pneumonia. At the same time, one remarked upon the improved condition of the right lower lobe. The dulness had diminished perceptibly, the respiratory murmur had regained much of its normal character, and/

and resolution was evidently in progress.

On December 4th, the child's condition showed slight improvement. There was less pain in the affected joints, and though the lung condition continued to give anxiety, the outlook was certainly more hopeful.

On December 6th, the wrist joints became affected. Like the knees, they became suddenly swollen and painful, as that she was quite unable to use them. Simultaneously she complained of a feeling of distress and pain over the region of the heart, and on examination one was able to detect a very definite change in the nature of the heart sounds. They had lost their clearness, and had become soft and indistinct. No murmur was audible, but over the base of the Ensiform Cartilage one could hear a faint systolic rub. The apex beat had become more diffuse, and the area of deep cardiac dulness was slightly increased. The temperature remained high, and the pulse was very rapid, of low tension and inclined to be irregular. Acute Rheumatic Pericarditis was diagnosed, and treatment ordered accordingly.

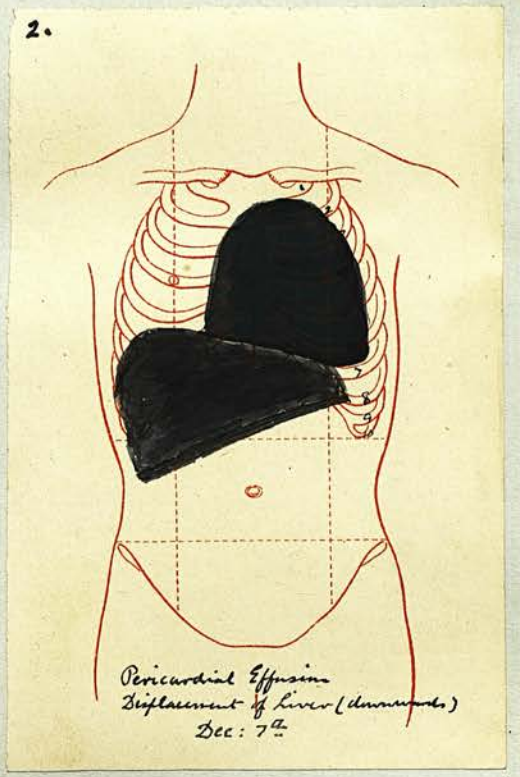
The condition of the child now became critical,/

critical, and it was evident that she was under the influence of a grave toxaemia. At this stage an exploring needle was passed into the Median Basilic Vein of the arm, and about half an ounce of blood withdrawn into the barrel of a sterilised syringe. This was carefully transferred to a flask of sterile ascitic bouillon and placed in the incubator. The results are fully recorded below.

On December 7th, pain and swelling in knee and wrist joints had practically subsided, and she began to be able to move these joints a little, The right lung continued to improve, but the left showed no signs of resolution. Its lower lobe remained totally consolidated, and that, together with the ever increasing amount of fluid in the pericardial sac, rendered the whole of the left side of the chest absolutely non-resonant and immobile.

The pain over the cardiac region became very acute, and this was aggravated by the incessant coughing. Twelve hours had made a marked difference in the size of the area of cardiac dulness. It had extended in all directions, but especially upwards and to the left, the upper border being in the second interspace. The dull area, when mapped out, assumed the shape of a truncated cone, with its base lying between/

between two points, one situated to the right of the lower end of the sternum, and the other outside the nipple line in the sixth interspace.



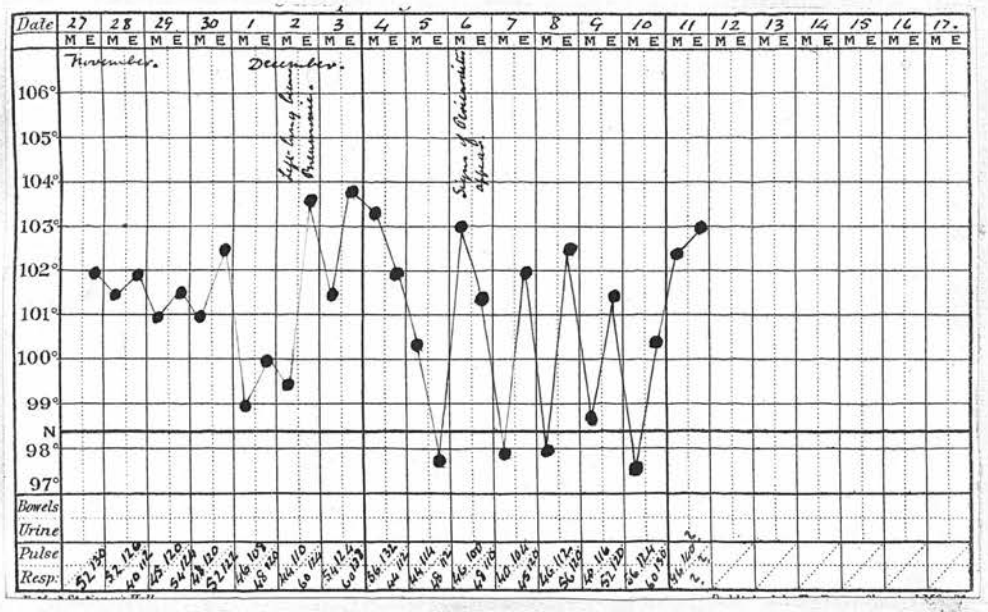
The lower border of the liver was depressed and could be felt about 2 inches above the umbilicus. At the autopsy this organ was found to be enlarged as well as displaced downwards.

On the 8th, the child's condition became very grave. The pericardial effusion had increased still more, until the intercostal spaces were obliterated, and the front of the chest presented quite/

quite a flat surface. The left side was now perceptibly larger than the right, and there was a distinct bulging over the precordia. The apex beat was completely lost, and the heart sounds could be heard only very indistinctly. The systolic rub was still audible at the sterno-xiphisternal junction, and that notwithstanding the fact that the upper limit of the fluid was at the second rib. This was taken to be a sign that the cardiac wall was still in contact with the pericardium and the anterior wall of the chest in this region, and because of this it was thought inadvisable to attempt paracentesis here. (This conclusion, as was shown at the autopsy, proved to be correct.) The lung condition remained the same as on the previous day.

On the 10th, matters had not improved, but rather had become more critical. The upper limit of the fluid now appeared above the second rib, and the whole of the left side of the chest seemed to bulge in front. The heart's action had become irregular and lacking in force. The pulse was small, weak and intermittent, with a rate of about 120 per minute. The child looked gray and anxious, and her appearance suggested the approach of heart failure. Her respirations had increased to 64 per minute, and were/

were shallow and laboured. She was evidently going rapidly downhill, and one saw that the end could not long be delayed.



The temperature remained high, but there was not and never had been throughout the whole illness any tendency to hyperpyrexia. One also remarked the entire absence of delirium during the course of the disease, and notwithstanding the condition of the lungs the unusual scantiness of expectoration.

On the 11th, she became rapidly weaker.

Her/

Her pulse was imperceptible at the wrist, her respiration short and gasping, and her heart sounds were almost inaudible.

On the morning of the 12th, she died, no alteration having taken place in the condition either of heart or lungs.

THE AUTOPSY.

A post-mortem examination of the body was made, of which the following is a description.

Rigor Mortis was well developed, and the body was fairly well nourished. The left side of the chest was more prominent than the right, there being a distinct bulging of the wall over the precordia. There were no other external signs worthy of note.

On opening into the chest cavity, the first thing to meet one's gaze was the pericardium enormously distended, and extending right from the sixth interspace to the second rib. The left lung was pressed right up against the thoracic wall by this large accumulation of fluid. The sac was opened, and about 20-25 ounces or more of blood-stained fluid allowed to escape.

It was noted that, whereas the parietal pericardium/

pericardium was quite stripped off the heart at the base and on the left side, it was still in intimate association and closely bound down to the heart wall on the right side. The parietal pericardium was thickened and inflamed throughout, and its inner surface was rough and covered with organising lymph. To the eye it presented the appearance of a raw surface, thickly covered with hair-like processes, which bled easily when torn. Its thickness was quite ¼ inch. It was firmly adherent to the diaphragm, to the anterior chest wall and to the left lung. Its attachment to the diaphragm and to the left lung was so intimate as to render it quite impossible to separate them without tearing and injuring these tissues. The pericardium, both visceral and parietal, presented the appearance of acute inflammation, which extended all round the heart, downwards on to the diaphragm, upwards on to the great vessels and backwards into the mediastinum. The heart presented the appearance of a red prickly pear within the pericardial sac.

THE HEART.

This organ was slightly enlarged; the right side dilated and filled with ante-mortem and post-mortem clot; the left empty. The walls were soft/

soft, and when cut into, presented a cut surface which looked dull and cloudy. The heart muscle was distinctly congested, the fibres looked to be swollen, and were kept apart by a thin layer of exudate, and the whole condition seemed to point to the presence of an acute myocarditis. In consequence the walls were friable and could easily be torn.

Inside, the endocardium had undergone a very marked change. The line of separation between it and the myocardium was blurred, and it seemed as though the two merged into each other. It had lost its natural lustre, and had become cloudy and granular in appearance. Its thickness was increased, and it felt somewhat spongy - especially so in the region of the valves and the chordae tendinae. Here and there, over the surface, was some sticky lymph-like exudate, especially well marked between the musculi pectinati. All this was evidently the result of an acute inflammatory process; in other words, there was a very marked endocarditis present. This had involved the whole of the endocardium on the right side, as well as on the left, and had extended well up into the aorta and pulmonary arteries.

All the valves were affected, the disease showing more on the aortic and mitral than on the tricuspid/

tricuspid and pulmonary - the last mentioned being the least affected.

The cusps of the aortic valve were opaque and turgid, and along their free margins was quite a crop of vegetation.

The cusps of the mitral valve were similarly affected, being covered with a lymph-like exudate and having a number of vegetations growing from the auricular surface and round the line of attachment.

On the right side the tricuspid valve had also suffered and over the auricular aspect of its cusps were a number of scattered vegetations, whilst the cusps themselves were distinctly swollen.

In the case of the pulmonary valve the effects of the disease were neither so extensive nor so marked, but nevertheless it had not escaped. Like the others it showed definite inflammatory changes and the margins of the cusps had lost definition.

The Chordae Tendinae were also included in the general change and had become distinctly swollen and enlarged and to some of them little vegetations were attached.

The vegetations on the valves were for the most part small, grayish-red in colour and covered with exudate. There was no necrosis nor ulceration present/

present in any of them.

The extent of involvement of the Heart and Pericardium was remarkable, no part of either having escaped.

Cultures were made from the pericarditic fluid and the surface of the pericardium and films were also made from the exudate and from the blood.

An aortic cusp with vegetations and a piece of the pericardium were removed for the purpose of having sections cut and stained. A description of these is given below.

THE LUNGS.

The Pleura was healthy on right side, and on the left was diseased only where it came into contact with the inflamed pericardium.

The right lung was congested especially at the base and contained a quantity of blood stained fluid, but otherwise it appeared healthy.

The upper lobe of the left was like the right lung distinctly congested, but showed no signs of consolidation. The lower lobe, on the other hand was quite solid throughout. When squeezed only a little blood-stained exudate appeared on the cut surface. The pericardium was firmly attached to this lobe and in separating the two, the lung was badly/

badly torn. The pleura all round this area of attachment was inflamed and covered with the same lymph-like exudate that was described in case of the heart. There was no attachment between pleura and chest wall. A piece of lung was cut out for sections. Films of the exudate were also made.

THE SPLEEN.

This organ was larger than normal and was exceedingly soft and friable. Scrapings were taken from it and cultures and films made therefrom.

THE LIVER.

This organ was displaced downwards and enlarged. Its lower border reached to within 2 ins. of the umbilicus. It was yellowish red over surface, and was distinctly mottled. When cut into it showed typical fatty degeneration, each little red lobule being surrounded by an area of yellowish coloured tissue.

THE KIDNEYS.

Both were congested but otherwise fairly healthy. In the pelvis of the left there was some purulent material. Films were made from this.

THE JOINTS.

The knee joints were opened and were found to contain some glairy, non-purulent material (Cultivations were made from it). The synovial membrane was/

was swollen and lustreless, but otherwise showed no very marked change.

All the other organs examined were healthy and taking a general survey of the case in the light of the clinical history and of the post-mortem findings, one formed the opinion that the child had suffered from an acute general infection causing disease in the organs above described, failure of the heart's action and death.

THE PATHOLOGY.

The following is a description of sections made from specimens taken from (a) Pericardium, (b) Aortic Cusp with Vegetations, (c) Pneumonic Lung.

All have been stained by Gram's Method.

(a) PERICARDIUM. (Slide I.)

The cells of the fibrous portion are opaque and very much swollen, their outline is blurred and their nuclei small and indistinct. Those of the serous portion shew a similar condition, only the cloudy swelling is much more marked. There has been a very definite change in the endothelial layer. It has been broken up and in great part has disappeared/

disappeared. The tissue underlying is infiltrated with leucocytes and fibrinous material, whilst on the free surface is a deposit of fibrin. Along this free edge and amongst the loose tissue one can discover a number of gram staining cocci. For the most part they are diplococci and short chained streptococci and they are found only amongst the cells and on the surface of the inner layer. They do not occur in clumps but are found more or less singly scattered throughout the tissue and along its edge.

(b) SECTIONS OF AORTIC CUSP WITH VEGETATIONS.

(Slide II).

The cells of the cusp show very definite cloudy swelling. Leucocyte infiltration has occurred between them and towards the surface an exudate of fibrin has tended to separate them still more. Attached to the cusp along its free margins are little masses of fibrin which constitute the vegetations. This fibrinous material is loose in character, areolated and along its attachment to the cusp it is becoming organised.

Short chained streptococci of the above mentioned type are to be found along the free edge of the cusp, amongst the loose fibrinous material and/

and in the zone of attachment to the cusp itself.

(c) SECTION OF PNEUMONIC LUNG. (Slide III).

The alveolar walls show increase in thickness due to inflammatory swelling, the capillaries are dilated and the alveoli themselves are loosely filled with leucocytes and fibrin, apparently a condition of Pneumonic consolidation undergoing resolution. Scattered throughout the section, particularly along the walls of the alveoli and within the leucocytes, are Gram-staining diplococci. These are non capsulated and probably are of a similar nature to those found in the pericardium and aortic cusp. Very few longer chains are to be found in the section.

THE SPUTUM. (Slides IV & V).

Several films were made during the progress of the case. These were stained, some by the Simple Methylene Blue method and others by Gram's method. The bacteria commonly found in samples of sputum were present, and in addition there was also a non-Gram-staining bacillus which, because of its abundance and its very definite characteristics, arrested attention. This particular organism seemed to be more or less diplobacillary in form, and it occurred both intra- and extra-cellular. At first it was thought to/

to be diplococcoid in nature, probably one of the Catarrhalis group, but its form was so definitely bacillary in some of the films that after repeated examination this idea was abandoned and the conclusion arrived at that it was a bacillus.

In the films examined it occurred, as has already been said, both inside and outside the cell, its length and thickness varying with its position. The intra-cellular forms were shorter, more coccoid in form, always double and they lost the Gram's stain less readily than the extra-cellular forms. The extra-cellular forms, on the other hand, whilst there was the tendency to be diplobacillary, were not constantly so, they lost the Gram's stain more easily and took on the Methylene Blue stain more tardily and less regularly. The short forms occurred chiefly within large cubical cells which probably came from the upper part of the respiratory tract - either pharynx or tonsils - rather than from the lung itself. These cells in some of the films examined were absolutely packed with the organism until scarcely a bit of the cell protoplasm could be discovered which was free from it.

Cultivations on Bouillon and Blood Agar were made from the sputum, and a non-Gram-staining bacillus/

bacillus similar to that described as being present in the films was isolated. This organism also had the tendency to grow in pairs, especially when grown on certain media; it stained only faintly and very irregularly with Methylene Blue and it readily lost the stain in Gram's method. It was grown on the various media at 37°C. and at room temperature, and after exhaustive investigation its cultural characteristics were found to correspond exactly with those of the bacillus present in the blood and which is fully described below under "Blood".

Its morphology also corresponded, being motile, non-Gram-staining and multiplying by transverse fission. From the collective evidence one was therefore driven to the conclusion that the two were really one and the same.

THE BLOOD.

As explained above, a specimen of the blood - about ½ oz. - was withdrawn from the median basilic on the 10th day of the disease. This was done with all due regard to the asepsis of the operation and to the absolute sterility of all the instruments used, as well as of the medium into which the specimen was received after withdrawal. The skin was thoroughly sterilised before making the puncture and/

and the blood was immediately transferred from the sterile syringe to a flask of ascitic bouillon which had been previously sterilised and incubated at 37°C. for three days without result. The whole was well mixed and put into the incubator at 37°C.. At the end of 12 hours there was a slight turbidity noticeable, especially towards the surface and around the edges of the fluid. After 24 hours there was a definite scum which spread completely over the surface of the fluid. Films of this were made and stained by Methylene Blue and Gram's method. A Gram negative bacillus was found to be present which from its small size and irregularity of staining with Methylene Blue struck one at first as belonging to the Influenza group. Its other characteristics, however, did not coincide with the Bacillus Influenzae.

A marked feature of the bacillus at this stage, and one which it partially lost in sub-cultivation, was its tendency to assume the diplobacillary form. It was also slightly curved, or rather the diplobacillus taken as one assumed the shape of a curve somewhat after the style of the comma bacillus. In size it varied from 1/u to 2/u long, with here and there a filamentous form of about 4/u in length. It/

It took on the Methylene Blue stain very slowly and very irregularly, so as almost to give it the appearance of being a Bipolar staining organism. This same appearance existed, though to a less extent, in films stained by Gram. It was actively motile and gave no indication of spore formation. At this stage the culture was thought to be a pure one as no other organism had been observed. A film made at the end of 48 hours, however, proved this to be incorrect, for in it was discovered a Gram + coccus along with the above mentioned bacillus. This coccus existed in small chains, usually of two or three, and was evidently one of the Streptococcus group. The culture was clearly a mixed one and steps were taken to isolate the organism. Subcultivations were made on Agar and from these plates were made and inoculated. Colonies appeared at the end of 24 hours, and from some of these at the end of 48 hours subcultivations were made. In this way one was able to separate the two organisms and obtain pure cultures of each. Having attained this much, one then proceeded to find out the cultural characters of each of the organisms as demonstrated by their behaviour on the various media when grown at different temperatures.

These/

These will now be given in detail, together with a description of their morphology and their respective fermentation characteristics when grown in the various sugar media.

THE BACILLUS.

ITS MORPHOLOGY.

SIZE AND SHAPE. (Slides VI, VII, VIII, IX & X).

The size varies considerably with the media on which it is grown and the temperature. In some it is long and filamentous, in others short and coccoid. Thus on Agar at 37°C. it is not more than 1/u or 1·5/u in length, whereas on the same medium at room temperature it may be as much as 2/u to 3/u, whilst on potato it may reach 4/u or 5/u. Its average is about 1·5/u to 2/u long and ·5/u in thickness. It is a curved rod with rounded ends, is non sporing and frequently exists in pairs.

MOTILITY..

The bacillus is actively motile. It possesses a terminal flagellum to which its motility is attributable. The organism when grown at room temperature is distinctly more motile than when grown at 37°.

ITS/

ITS VITALITY UNDER VARIOUS CONDITIONS.

It resists high temperature badly. It ceases to grow at 45°C. and dies at 60° - 65°C. Low temperatures it stands fairly well. Freezing arrests growth and if prolonged causes the death of the bacillus.

Drying, up to a certain point, merely has the effect of causing it to assume irregular forms. Beyond that point it rapidly succumbs.

All disinfectants are inimical to its life.

ITS STAINING CHARACTERISTICS.

It stains very reluctantly with Methylene Blue, requiring from twenty to thirty minutes' contact with the stain to produce a satisfactory result. Some parts of the protoplasm take on the stain more readily and therefore show up better than others. This is especially characteristic of cultures grown at 37°C. and upwards, but it is not altogether absent in the cultivations made at lower temperatures. This feature gives it an irregular appearance which in some cases closely resembles Bipolar staining.

With Gram's method the same irregularity of staining, though still noticeable in some specimens, is not nearly so well marked. One does come across individual bacilli in a field which appear more/

more darkly stained at the poles than in the centre and might quite correctly be called Bipolar. These forms occur very frequently in certain cultures. The distinctive stain of the method is not retained, that is it is Gram - .

CULTIVATION OF THE BACILLUS ON ARTIFICIAL MEDIA.

AGAR PLATE at 37°.

Colonies appear at the end of 12 hours as tiny, slightly opaque discs about the size of a pin's head. In 24 hours these increase in size and measure about one millimetre in diameter. Their opacity also increases and they develop a distinct greenish fluorescence. There is no change in the surrounding medium. When viewed under the low power ($\frac{1}{4}$th) of the microscope one of these colonies presents a discoid appearance with a clear, well defined and regular margin and a dark granular centre. The colour is greenish towards the periphery, but towards the centre where the colony is thicker and the granules more dense it is dark brown. There is a good deal of "heaping up" in the centre which gives to the colony in that region a more or less homogeneous appearance, but as one proceeds outwards towards the periphery the granular appearance becomes more and/

and more distinct. But the granules do not extend quite to the periphery; they stop short of it by a well defined area within which there are no granules at all. This is the clear area of the colony.

About the deep colonies there is nothing very distinctive. They are merely little round masses about $\frac{1}{16}$ m.m. in diameter, dark brown in colour and quite opaque.

STROKE CULTURE ON AGAR 37°C.

The bacillus grows fairly profusely at this temperature. Twelve hours after inoculation there is a distinct semi-transparent growth along the track of the needle. At the end of 24 hours the growth is much more distinct, more opaque and has developed a greenish fluorescence. This colouring does not as a rule extend to the medium, though it has been noted that its tendency to do so is greater when grown in the light than when grown in the dark and at 37°C. than at 22°C.

The streak has a wavy edge, is thicker towards the middle, and if left undisturbed does not tend to spread out over the surface of the medium. When looked at in ordinary daylight the growth has a greyish appearance; the surface is uniform, smooth and glassy, and it resembles more than anything else a streak of thin mucus. The green colour is not noticed/

noticed unless when held up to the light, except in cultures kept at 37°C. for 48 hours or more where the medium has taken on the colour also. As the growth gets older its opacity increases, but it does not change colour. After 24 hours it develops a distinct faecal odour. This is more marked in the liquid than the solid media.

AT ROOM TEMPERATURE.

It grows very well. The character of the growth itself is similar to that described above, but it has a more definitely wavy edge and does not show the green colour so well. The medium does not become coloured at all at this temperature.

GELATINE (STAB) AT ROOM TEMPERATURE.

Grows well and causes liquefaction of the medium. Solution begins at the end of 12 hours in the stab of the needle and in one or two days has spread out to the sides of the tube. Then it continues down the medium until the whole is liquefied. On the surface of the liquefied portion there is a slight scum. Underneath this there is a cloudy area and at the bottom of the liquid portion and resting on the top of the solid is a thick, whitish deposit. In the first day or two after inoculation liquefaction proceeds very rapidly, more slowly after that. No

green/

green colour is developed in the medium.

GELATINE (STROKE).

A gutter due to liquefaction of the medium forms along the track of the needle 12 hours after inoculation. This gradually extends until the whole is liquefied.

BOUILLON AT 37°C.

Grows well. At the end of 24 hours there is uniform turbidity in the medium with a whitish sticky deposit at the bottom and a distinct scum on the surface of the liquid.

The scum has a slight greenish tinge and tends to grow up the sides of the tube. There is no colour in the rest of the medium either when grown at 22°C. or at 37°C. The medium becomes quite opaque three or four days after growth has commenced. It possesses a marked faecal odour.

POTATO AT 37°.

At the end of 12 hours there is a shiny, sticky looking growth which is quite devoid of colour. In 24 hours it becomes more or less cream-coloured and more abundant. In 48 hours the growth exactly resembles that of Glanders, being honey-like in colour and consistence. After this the colour gradually deepens, becoming darker and darker brown, until at the/

the end of a week it resembles "brown sugar". The potato is not coloured.

When grown on this medium the bacillus attains a much greater length than it does on any of the others. It becomes quite filamentous, but at the same time much more slender.

MILK AT 37°.

In this medium the bacillus grows well but does not cause clotting. After about three days flocculi appear in it and a greenish deposit collects at the bottom. It remains alkaline in reaction.

BLOOD AGAR AT 37°.

When grown in any medium containing blood it evinces a tendency to absorb the colour from the blood. This is well seen in a plate culture made from Blood Agar. Around each separate colony there is a clear area from which the haemoglobin has been subtracted. In consequence of this the colonies are much darker in colour.

If grown in conjunction with the streptococcus described below it rapidly disappears, being killed out by that organism in from three to ten days after inoculation.

FERMENTATION/

FERMENTATION TESTS OF BACILLUS.

Sterile tubes containing Solutions of various sugars were inoculated with the bacillus and incubated at 37°C. to test for the production of Acid and Gas. In the following table the names of the sugars used together with the results of the tests are set forth.

IN the table: A = Acid; G = Gas; 0 = No change; A++ = Acid well marked; A- = Alkaline; C = Clot.

Glucose.	Lactose.	Maltose.	Raffinose.	Inulin.	Dulcite.	Mannite.	Lit: Milk.
(After 24 hours.)							
A+	0	0	0	0	0	0	0
(After 48 hours.)							
A++	0	0	0	0	0	0	Flocculi green deposit. No acid.
(After 4 days)							
A++	0	0	0	0	0	0	Same. No acid.

After 10 days no further change had taken place.

Neutral Red was inoculated and on fifth day it was reduced. It was scarcely altered after first 24 hours, but at the end of 48 hours there was a distinct change. At first the medium became reddish-yellow in colour and then it gradually lost the red tinge altogether, remaining of a yellowish brown hue.

INDOL.

The/

The Bacillus was grown in peptone water, and the same after 48 hours' incubation was tested for indol. The result was negative.

ANIMAL EXPERIMENTATION.

The Bacillus carefully grown and prepared was injected into one of the veins of a Guinea Pig. On the second day after injection the animal appeared ill but did not succumb. It recovered entirely and shewed no ill effects afterwards.

One, therefore, concluded that it was a non-pathogenic organism and that, per se, it played no active part in the death of the child.

THE STREPTOCOCCUS.

ITS MORPHOLOGY.

SIZE AND SHAPE. *Slides XI & XII.*

From the frequency with which this special micro-organism occurs in diplo form one might call it a diplococcus, but as it also occurs in short chains of three or four, perhaps it is better to call it a Streptococcus of the "brevis" variety. The size of the chains depends to some extent on the medium on which it is grown and the temperature - thus if grown in Broth at 37°C. one gets longer chains than if grown on Agar or Gelatine. As a rule the longest chain/

chain is composed of four or five, and the shortest of two cocci.

Each individual coccus measures about 5/μ in diameter and multiplies by fission.

MOTILITY.

It is non-motile. In a hang-drop preparation the only movement seen is Brownian.

VITALITY.

It resists high temperatures badly and dies out in culture very soon. 45°C. to 50°C. arrests growth whilst a temperature above 55°C. quickly causes death. Cold it resists much better but drying is almost instantly fatal.

STAINING CHARACTERISTICS.

It stains well with Methylene Blue - a short exposure to the stain being sufficient to give a good result.

With Gram's method it takes up and retains the stain well, that is Gram +.

CULTIVATION/

CULTIVATION OF STREPTOCOCCUS ON ARTIFICIAL MEDIA.

AGAR PLATE 37°.

In 48 hours small circular colonies appear on the surface of the medium. Previous to the second day they are not visible to the naked eye, though at the end of 24 hours they may be seen by the aid of a magnifying glass. The colonies are slightly raised, and, though at first almost transparent, they soon become opaque with a tinge of green about them. In size they measure from ½ to 1 m.m. across and reach the maximum in about 36 hours; after that period they make no further appreciable increase.

Examined under the low power of the microscope the colonies present a fairly regular outline (they are not always quite circular), a clear homogeneous zone at the periphery and a dark granular centre, the growth is much thicker at the middle than it is at the periphery and the granules only extend out as far as the "clear area". This area constitutes about one third of the whole extent of the colony.

DEEP COLONIES.

The deep colonies are dark brown in colour and irregular in outline. They are so opaque that no details of their structure can be seen.

AGAR STROKE AT 37°

At the end of 12 hours one can just discern a number of small transparent discrete colonies along the track of the needle. In 24 hours these have coalesced/

coalesced to form a continuous streak. By 48 hours the growth has become more marked and quite opaque. It is of uniform thickness all the way up the streak and possesses an irregular margin. The colour is greyish and it is best seen by holding the tube in the light against a dark background. After about 10 days or so the growth begins to disappear, and in 14 days it has almost entirely vanished.

AT 22°C.

The organism grows very slowly at this temperature and after 7 days only a very thin growth appears along the needle track. The colonies tend to remain discrete from the first and they are more transparent and dew-drop like in appearance than in the growth at 37°C.

GELATINE (STAB) AT 22°C.

Growth appears after 24 hours, confined at first to the upper part of the stab and then gradually descending along the stab forming a fine white streak in the substance of the medium. Along this numbers of tiny white processes project out into the gelatine and give to it rather a distinctive appearance somewhat resembling that seen in the Tetanus group, only much less pronounced. At the lower extremity of the stab there may be one or two quite discrete colonies. The medium is not liquefied.

GELATINE/

GELATINE (Slope) at 22°C.

Beautiful transparent, almost crystalline colonies appear after about 48 hours. These are discrete and remain so. Growth is scanty and is confined strictly to the needle track. This is perhaps the most distinctive growth of this organism.

BROTH at 37°C.

There is slight turbidity noticeable in the medium after 12 hours, more marked after 24 hours, reaching its maximum in 48 hours. The turbidity is uniform throughout. At the same time a granular deposit forms at the bottom of the tube.

POTATO at 37°C.

Slight growth occurs at end of 48 hours. It is thin colourless, scanty and not at all distinctive.

MILK at 37°C.

After 24 hours there is slight clotting of the medium and it gives an acid reaction. In 36 hours this passes off, the medium again becomes alkaline and the clot is redissolved.

If/

If grown on any medium containing blood, the colour of the blood is rapidly changed, becoming quite black. This seems to be due to some power which the Streptococcus possesses of acting upon the oxy-haemoglobin and changing it into methaemoglobin.

FERMENTATIVE REACTIONS OF THE STREPTOCOCCUS.

(After 24 hours at 37°C.)

GLUCOSE.	LACTOSE.	MALTOSE.	RAFFINOSE.	INULIN.	DULCITE.	MANNITE.	LITMUS MILK.
++	0	++	+ or −	0	0	++	+ Slight clot. Lower portion of liquid dirty green col. with a green deposit.

(After 48 hours at 37°C.)

++	+	++	0	0	0	++	++ Slight clot as above.

(After 72 hours at 37°C.)

++	++	++	0	0	0	++	− No clot as it was at first.

(After 7 days at 37°C.)

++	++	++	0	0	0	++	− As at first.

	NEUTRAL RED.	PEPTONE WATER.
AFTER 48 hours at 37°	Slight reduction.	No Indol.
After 72 hours at 37°	Returned to its former colour.	(− = alkaline (+ = acid (++ = markedly acid (0 = no change.

EXPERIMENTS/

EXPERIMENTS ON ANIMALS.

INOCULATION WITH STREPTOCOCCUS.

A ~~guinea pig~~ rabbit was inoculated intravenously with the streptococcus. It died on the sixth day following the inoculation. A post mortem examination was made and specimens of the blood taken. Cultivations from these proved the presence of a Streptococcus, which on examination was found to be the same as that injected.

The heart was examined and found to be free from disease though the streptococcus was recovered from the blood in its cavities. Liver and spleen were congested, but otherwise healthy. There was a typical acute arthritis affecting all the joints, and when these were opened into, a glairy, non-purulent fluid escaped. This contained numbers of leucocytes, chiefly polymorphonuclears and lymphocytes. From it also the streptococcus was recovered in culture. Infarcts were present in both kidneys, probably the result of pyaemia set up by the organism. From the recorded results one had no hesitation in saying that the organism in question was pathogenic and

that/

that it was the cause of the disease.

PERICARDITIC FLUID.

Specimens of this were taken at the autopsy and cultures made therefrom. The Streptococcus already described was isolated.

Films were also made and stained and found to contain large numbers of leucocytes - chiefly the polymorphonuclear and lymphocyte varieties - and red cells. In one or two of the films a few scattered diplococci were found, but were not in sufficient numbers to be easily demonstrable.

JOINT FLUID.

Here again cultures were made from the fluid obtained from the joint cavities and in some of these the streptococcus was present and was subcultivated. Its cultural and other characters were exactly the same as those of the Streptococcus described under Blood. Films of the fluid were also made and stained, but without very definite results. One or two isolated diplococci were found, but not in any demonstrable number, yet sufficient to prove the presence of the organism.

SPLEEN/

SPLEEN, LUNG AND PERICARDIUM.

Both films and cultures were made from the substance of the spleen, but in each case the result was negative. The same holds good in case of the lung exudate.

In a film made from a scraping taken from the Pericardium a few small streptococci were found for demonstration, of which see "Section 2."

KIDNEY.

Pus was found in the pelvis of the left kidney and from it films were made and stained. No organisms of any kind whatever were found. Cultures were not made in this instance.

T H E/

THE DISCUSSION.

The case just described is remarkable for three reasons.

(1) The mode of onset and acuteness of the symptom.

(2) The nature and extent of the damage done.

(3) The peculiar nature of the infection.

(1) It is rare to hear of an attack of Acute Rheumatism being ushered in with symptoms of Lobar Pneumonia. And yet so it was in the case above described. The child's illness commenced with pain over the right side of the chest and evident physical signs of Pneumonic consolidation of the right lower lobe. After lasting some days these signs disappeared, the consolidation resolved and the lung returned to its normal healthy condition. But recovery did not take place before the left lung also had begun to show signs of involvement, and in a short space of time its lower lobe became consolidated and pneumonia set in with all its characteristic signs and symptoms. Then the pericardial trouble commenced and though it is highly probable that the disease had already set in, in the pericardium at the time of involvement of the left lung, no indications of this were given.

With/

With such evidence before one the first question which naturally occurs to one is "What was the cause of the Pneumonia; was it Pneumococcal or was its origin the same as that of the Pericarditis?" A satisfactory answer to these queries is difficult to find. From the known facts that (a) over a considerable area the diseased lobe of the left lung and the pericardium were in intimate association so that any infection might easily travel from the one to the other and (b) that in the sections made from the affected lobe a few short streptococci (which certainly did not seem to be pneumococci) were found, one is inclined to conclude that the causal agent of both conditions was the same, viz., the Streptococcus Rheumaticus. If this were so, the circumstance is unique.

A striking feature of the case was the severity of the local manifestations without the presence of any urgent constitutional symptoms. Thus throughout the whole course of the disease the temperature never rose much above 102·5 °F., the pulse rate maintained a steady mean of about 120 to 130 per minute and the respirations, though sometimes as rapid as 60 to 70 per minute, kept as a rule about 40 to 50.

To/

To the fact that at no time did the fever ever reach a point above 130°F., one must attribute the entire absence of delirium and the well sustained mental vigour of the patient. Right up till death the symptoms were quite over-shadowed by the gravity of the physical signs. This is not an uncommon occurrence in cases of rheumatic fever in children. I have known children with the most trivial symptoms of rheumatism to have the very gravest and most urgent cardiac and other lesions. The reason for this seems to lie in the predilection of the Rheumatic germ for certain tissues of the body and to the possibility that there is not always a general toxaemia of any importance.

Rheumatism is rarely a fatal disease in children (Holt) and that, I think, is the experience of most clinicians. In the above case it was fatal and rapidly so, and its fatality was in all probability due to the effects of a stronger than ordinary dose of the bacterium affecting the lungs as well as the walls and valves of the heart.

(2) The nature and extent of the damage done. When at the autopsy one surveyed the damage wrought to the lungs, heart, and pericardium, pleura, diaphragm liver, spleen, kidneys and joints one could not but be/

be impressed by the magnitude of it. It was no superficial mischief either; it was deep-set, real, and in many of the organs irreparable and permanent. Had the patient escaped with her life she must certainly have fallen victim, sooner or later, if not to a second attack of the disease, making fresh inroads on her resources, then to cardiac incompetence the result of the extensive damage done to that organ by the first attack. One remarkable feature of the case was the involvement of the right side of the heart. This is unusual even in very severe cases, and is further proof of the acute nature of the disease.

In face of such devastations what matters it by what name one calls the causal organism or whether it be the same as, or different from, some other *like* organism? All that matters is, that it does exist and that there is urgent need for means to be found of preventing its ingress to the tissues.

(3) The peculiar nature of the infection. The evidence accumulated in the above case is sufficient to warrant one promulgating the opinion that the causal agent of the disease was a micro-organism, and that micro-organism a streptococcus.

The fact that it was isolated from the heart/

heart, the pericardial fluid, the joint fluid and the blood proves conclusively that it was a possible cause of the disease, and its inoculation into an animal with fatal results and the subsequent recovery of the micro-organism from the animal's blood and joint fluid leaves no room for further doubt that it was the causal agent.

The remarkable features about this micro-organism were (a) its wide-spread prevalence in the tissues, (b), the disastrous effects which it had on certain of these by reason of the acute inflammation set up by it in their substance, (c) the possibility of its having been causal of the Pneumonia, (d) its association in the blood with another organism, viz., a nonpathogenic bacillus, for a short period in the course of the disease.

(a) It is seldom that one is able in a single case to demonstrate the presence of the streptococcus or any other germ in so many of the tissues, or so well, as one has been in this. Nor did one experience much difficulty in effecting the isolation. The organism abounded free and in such numbers in the various fluids that one was able in a few instances to demonstrate its presence by means of films of the fluid fixed and stained appropriately.

(b) Mention has already been made of the havoc played/

played by the organism and its toxins upon certain of the body tissues and also

(c) of its probable causal relationship to the Pneumonia.

Nothing further will, therefore, be said on these points.

(d) Concerning its association with a non-pathogenic bacillus in the blood, a great deal could be said, a little of which might possibly be the truth, but much would, of necessity, be mere conjecture.

In the first place, it is necessary to consider the nature of the bacillus and whence it came.

In its morphological and cultural characters it somewhat resembles Bacillus Pyocyaneus, and is in all probability a member of that group. The group is a fairly large one and numbers many unknown and unclassified organisms amongst its members. This is probably one of the "unknowns". Invasion of the blood and tissues by members of the group is not of infrequent occurrence, and, of late years in America and in this country as well, a good deal of attention has been devoted to the subject. Articles dealing with the matter have appeared from time to time in the American and also, to a less extent, in our own medical journals. It is, therefore, not altogether/

altogether new.

In the above case the organism was represented in two only of the body fluids, viz., the Blood and the Sputum. From both of these it was successfully isolated, subcultivations made and the life history of each worked out as far as possible. The results obtained were exactly similar for both, so the conclusion arrived at was that the two were one and the same organism.

Keeping the above in mind, the question now arises, "How did the bacillus get into the blood?" Was it introduced accidentally during the withdrawal of the specimen from the patient's arm or during its transmission between the arm and the culture flask? This is conceivable, but scarcely likely, because the most scrupulous care was observed during the process to prevent contamination from the skin or instruments and to preserve the absolute purity of the specimen. And if it were so the evidence of the sputum that the organism existed elsewhere in the body than in the blood has to be met, and this evidence cannot be dismissed lightly or regarded as merely coincidental. There is more than mere coincidence here, there is strong presumptive evidence that the organism in question did for a time inhabit the blood stream and that its presence there had some definite connection with/

with the presence of the same organism in the sputum. What was this connection? It was probably causal, and if so herein lies the explanation of the presence of the organism in the blood and also the answer to the question of how it gained admission thereto.

It is a well known fact in the medical and surgical world to-day, that a septic condition of the mouth and pharynx, or of both, can and does very frequently infect the whole body through the blood stream. This is precisely what may have occurred here for, in all patients, and especially in children who have had their natural defences either weakened or altogether destroyed by disease, the mouth, never at the best of times very sterile, becomes a very fertile source of infection.

The deduction which one makes, therefore, is that the Bacillus, already proved from examination of the sputum to be present in the throat, migrated therefrom, probably through the tonsils, into the blood and infected the blood-stream. Once into the vessels the debilitated condition of the patient allowed it to grow and multiply until it died out, either by reason of the unsuitability of the medium or because it was killed by the streptococcus.

The/

The latter is probably the correct reason, because several experiments made of growing the Bacillus and Streptococcus together on different media in every case resulted in the Bacillus disappearing in from three to ten days after inoculation.

One may take it, then, from the evidence produced that the blood-stream was infected from the throat, another proof of the great importance of the mouth as a factor in the spread of disease. It will not be out of place to state here that evidence of the presence of this same bacillus in the sputa of several other cases, the majority of whom were children, has been found by myself. This goes to prove that it is no uncommon thing to find this bacillus inhabiting the mouths and throats of children during disease.

Now we must consider the effect, if any, which the presence of this Bacillus in the blood had upon the progress of the disease. In my opinion and in the opinion of others who saw the case, its presence had little if any effect on the progress of the disease. It certainly may have added to the exhausting influence at work in the patient's body, but it did not in any way materially affect the prognosis.

To complete the Bacteriological Discussion of/

of the case one must say a word or two on the particular type of Streptococcus discovered in the blood. It conforms both in its morphology, its cultural characteristics and its fermentative reactions to that discovered and described by Poynton and Paine and also by Beattie. It does not exactly coincide in all respects with it, but it comes so near that one has little hesitation in saying that it is a close ally, probably a member of the same family.

To summarise shortly: - the above case is interesting and instructive, -

(a) CLINICALLY because of -

(1) The nature of the onset of the disease, its severity and short duration.

(2) The curious intermingling of symptoms and constant change of interest from one to the other organ as these became involved in turn.

(3) Occurring in a child its rapidly fatal termination.

(b) BACTERIOLOGICALLY because of -

(1) Presence of (?) Streptococcal pneumonia.

(2) /

(2) Presence of Streptococcus in blood-stream and in many of the other tissues.

(3) Presence of another organism in the blood stream other than the one responsible for the disease.

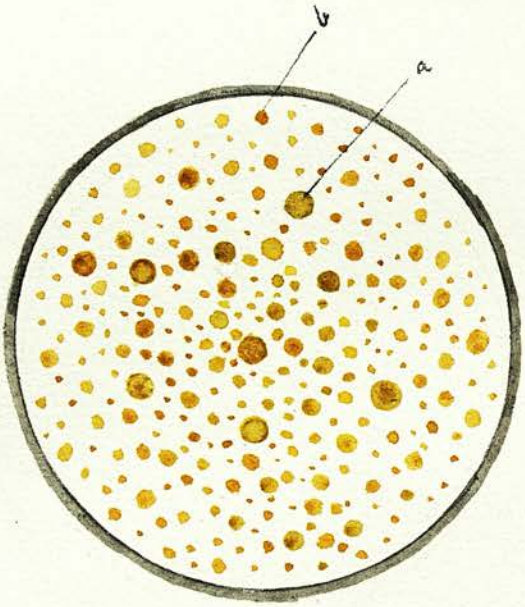
(4) The relationship which this "other" organism bore to a bacillus isolated from the throat of the patient, and the possible invasion of the blood-stream by this organism through the mouth.

The inoculation experiments on animals in the above, were done under the direction of Professor Beattie of Sheffield University, to whom I am much indebted.

---

over.

1.



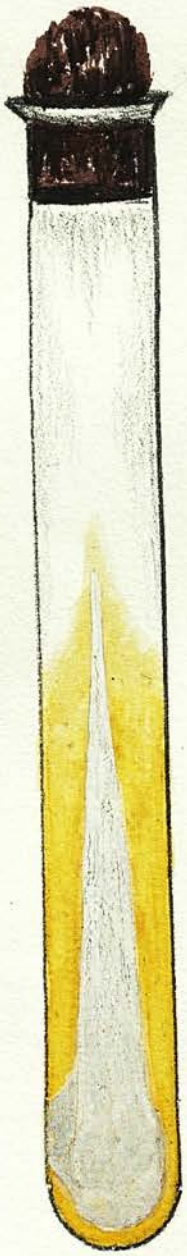
Bacillus

Agar-Plate at 37°C.

a. Surface Colony.

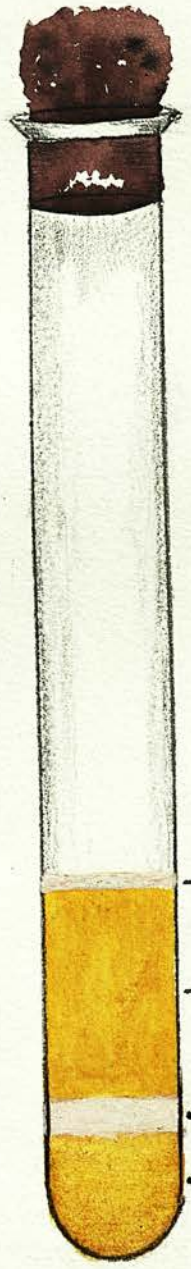
b. Deep Colony.

2.



Bacillus
Streak on Agar.
22°C.

3.

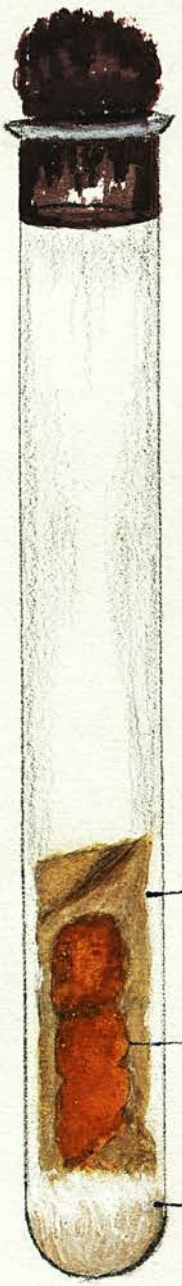


Bacillus.
Gelatine Stab
22°C.

- Whitish Scum
- Liquefied turbid medium.
- Whitish deposit
- Non-liquefied medium

Bacillus
in Bouillon
37°C.

5.



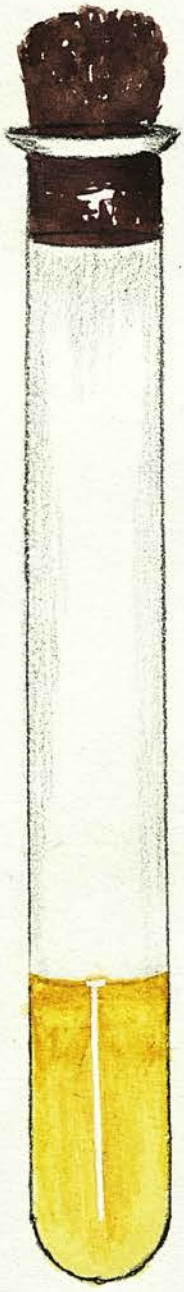
Bacillus.
on Potato.
at 37°C for 7 days.

6.

Streptococcus.
Double Streak on Agar.
at 37°C (3 days.)

The colonies have coalesced to form a continuous streak.

7.



Streptococcus.
Gelatine Stab.
22°C.