as urgent, and were sutured or stopped up, so far as possible. A few operations were done for primary haemorrhage either from the parietes of the chest or from the lung. In the cases arriving at the base aspiration was adopted for haemothorax, and closed drainage was carried out only when infection became clearly established. A few instances of pressure pneumothorax were treated by needling.

Conclusion

It must be admitted that any general experience of active surgery during the Battle of France was so limited by events that no definite conclusion in advance of our existing knowledge can be drawn from it. I would say that wound excision as a general principle still stands as the surgeon's sheet anchor. In sulphonamide and its derivatives we undoubtedly have allies of considerable power; we are not yet clear how far they should be regarded as adjuncts to surgical treatment or to what degree they may replace it. It is clearly desirable that controlled experiments should be planned in order to determine the value and the optimum dosage of the sulphonamide group of drugs, both in prophylaxis and in the treatment of missile injuries.

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HAEMOLYTIC STREPTOCOCCI IN THE CARDIAC LESIONS OF ACUTE RHEUMATISM

BY

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The aetiology of acute rheumatism has not yet been exactly defined, and the ravages of this crippling disease justify an even greater amount of investigation into the problem than has been given.

The haemolytic streptococcus has been regarded as the causal agent because of the obvious relation of acute rheumatism to a preceding acute tonsillitis occurring usually about two weeks before the onset of the rheumatic syndrome. This antecedent tonsillitis is known to be caused by the haemolytic streptococcus, and most patients in the early stages of their attack of rheumatism still harbour large numbers of haemolytic streptococci in their throats even though they have recovered clinically from the throat infection (Coburn, 1931; Collis, 1931; Schlesinger, 1930; Green, 1938; McCulloch and Irvine-Jones, 1929). Haemolytic streptococci are, of course, found in large numbers in the throat for a few weeks after clinical cure of any uncomplicated attack of tonsillitis. Moreover, outbreaks of rheumatic fever amounting to minor epidemics have occurred in semi-closed communities where streptococcal tonsillitis has been epidemic (Bradley, 1932; Glover, 1930; Schlesinger, 1930; Grenet, 1920; Glover and Griffith, 1931).

Such findings, although only indirect evidence, cannot be overlooked in spite of the large number of failures to recover any specific organism from the heart lesions or from the joint fluids. For this reason a search has been made for a filterable virus, and claims that such a virus

exists have been made by Schlesinger *et al.* (1935) and by Eagles *et al.* (1937).

Recently a more determined attempt has been made to recover a haemolytic streptococcus from the cardiac lesions of acute rheumatism even although the pathological appearances in the heart are not similar to streptococcal lesions in other tissues. A difficulty in such bacteriological investigations is that very few patients die in the acute stage. Green (1939) reported results in 9 such cases, and he was successful in all but one in cultivating haemolytic streptococci from those valves which showed vegetations, while no haemolytic streptococci were isolated from undamaged valves. Moreover, the streptococci isolated from different areas in any given case, including the throat strain, were of the same type (Griffith). The blood (post mortem) from such cases yielded no streptococci. Control cases never yielded haemolytic streptococci. Collis (1939) recovered haemolytic streptococci from 22 damaged valves collected from 17 cases of rheumatic fever.

Such evidence suggests an actual infection of the heart valves with haemolytic streptococci. We have continued this work, and the results of a series of 10 necropsies are reported.

Methods

The necropsies were performed as soon as possible after death, but in some cases twenty-four hours had elapsed and contaminants (nearly always coliform bacilli) were common in the material examined. After the thorax was opened the outer layer of pericardium was seared with a hot iron, and blood was removed from the cardiac chambers with a capillary pipette passed through the seared surface. The pericardium was opened through the seared area and some fluid removed for culture. Cultures were made also of any free pleural and peritoneal fluid. If there was a sero-fibrinous pericarditis pieces of fibrin were excised for culture. The surfaces of the liver and spleen were likewise seared and small pieces taken for culture.

The heart was then removed and opened as aseptically as possible after searing the surface. Cusps from the valves and a piece of myocardium were excised. In some of the cases these specimens were washed in alcohol before cultures were made. A throat swab was taken (post mortem), and on occasions the tonsils were removed for dissection and culture. In one case, in which the patient had died of chorea, the surface of the temporal lobe of the brain was seared and a little brain pulp aspirated with a pipette.

The culture medium used was the rich broth (from trypsin digest of horse muscle) described by O'Meara (1934), and subcultures were made after six hours, eighteen hours, and daily thereafter. Haemolytic streptococci grow most profusely in this medium in a few hours, and much of the success of the results was dependent on the fact that a subculture was made six hours after incubation. Frequently haemolytic streptococci were obtained in abundant growth by subculture or blood agar from the six-hour broth culture. Later subcultures from the original culture yielded only a few streptococci, which were difficult to isolate from contaminating bacteria. Case I, which is described to illustrate this, is a typical example of this observation, noted also by Green, who used the same technique (personal communication).

In 5 of the cases special methods were tried in an attempt to inhibit the growth of coliform bacilli. Heart valves and other tissues were cultured in broth containing sodium azide, and crystal-violet blood plates were used for subculture, but these methods did not yield as good results as that described above. Similar methods were adopted in 10 control cases.

Results

Ten fatal cases of acute rheumatism were examined post mortem and haemolytic streptococci were recovered from the hearts of 5. A very brief description of each case is given to correlate the clinical, pathological, and bacteriological findings. In the table which accompanies each case the use of a "positive" sign to indicate the presence of a lesion on a heart valve is restricted to acute lesions. In the case of lesions in the myocardium the "positive" sign is used to indicate the presence of Aschoff nodes without any attempt to indicate the exact age of such a lesion.

Case I

The patient, a boy aged 13, had had rheumatic fever in 1934. By 1938 there was an established mitral stenosis and aortic incompetence. He was admitted to hospital in 1939, and after a month died with advanced congestive heart failure. While in hospital the patient was afebrile.

At necropsy the pericardium showed signs of old pericarditis with a superimposed acute attack. Old rheumatic lesions were present on the mitral and aortic valves, with acute endocarditis on the mitral, aortic, and tricuspid valves.

Pathological Findings

	Naked Eye	Microscopical	Growth of Haemolytic Streptococci
Pericardium	+	+	—
Aortic valve	+	+	+
Mitral valve	+	+	+
Pulmonary valve ..	—	—	—
Tricuspid valve ..	+	+	+
Myocardium	—	+	+

Blood, spleen, liver, pericardial fluid, and pleural fluid did not yield a growth of haemolytic streptococci.

It is of interest to note that the subcultures from the six-hour broth culture of aortic, mitral, and tricuspid valves yielded haemolytic streptococci in very rich culture with only a few colonies of coliform bacilli. The plating from the aortic valve after eighteen hours yielded two colonies of haemolytic streptococci and an abundant growth of coliform bacilli; the mitral and tricuspid valves yielded only one colony of haemolytic streptococci and similar contaminants.

Case II

This patient, aged 13, developed typical rheumatic fever with chorea one week after tonsillitis. Severe febrile reaction persisted till death occurred one month later.

At the post-mortem examination the mitral and aortic valves showed an acute rheumatic endocarditis. The pulmonary and tricuspid valves and pericardium were healthy.

Pathological Findings

	Naked Eye	Microscopical	Growth of Haemolytic Streptococci
Pericardium	—	—	—
Aortic valve	+	+	+ (Type I)
Mitral valve	+	+	+ (Type I)
Pulmonary valve ..	—	—	—
Tricuspid valve ..	—	—	—
Blood	—	—	+ (Type I)
Brain	—	+	+ (Type I)
Myocardium	—	+	—

* Non-specific inflammatory areas in region of basal ganglia.

An α type of streptococcus was isolated from the spleen. The other tissues yielded only coliform bacilli.

Case III

The patient, a girl aged 11, had an attack of tonsillitis and developed acute rheumatic fever with joint pains after a week. She was immediately removed to hospital, where she was found to have an active endocarditis. The patient became cyanosed and dyspnoeic, and died after one week with a dilated heart.

A necropsy showed that there was an old rheumatic endocarditis of the mitral valve with stenosis, with acute lesions superimposed. The other valves and the pericardium were healthy.

Pathological Findings

	Naked Eye	Microscopical	Growth of Haemolytic Streptococci
Pericardium	—	—	—
Aortic valve	—	+	+
Mitral valve	+	+	+
Pulmonary valve ..	—	—	—
Tricuspid valve ..	—	+	+
Spleen	—	—	—
Throat	—	—	+
Myocardium	—	+	—

* An unsatisfactory specimen.

The other tissues gave a growth of coliform bacilli.

Case IV

This patient, a boy aged 12, had been ill for three weeks at home with vague pains. Precordial pain and friction developed while in hospital but disappeared before he died of cardiac failure two months later. He was febrile throughout his stay in hospital.

At the necropsy there was an acute pericarditis with adhesions between the two layers in places. The inflammation appeared to be regressing.

Pathological Findings

	Naked Eye	Microscopical	Growth of Haemolytic Streptococci
Pericardium	+	+	—
Aortic valve	—	+	—
Mitral valve	—	+	+ (Type II)
Pulmonary valve ..	—	—	—
Tricuspid valve ..	—	—	—
Blood	—	—	+ (Type II)
Throat	—	—	+ (Type II)

Case V

A girl aged 5 had tonsillitis with joint pains three weeks before admission to hospital. She developed chorea and was admitted to hospital with signs of pericarditis. She died after a total illness of three months due to congestive heart failure.

At necropsy acute pericarditis and acute endocarditis of all the valves were present.

Pathological Findings

	Naked Eye	Microscopical	Growth of Haemolytic Streptococci
Pericardium	+	+	—
Aortic valve	+	+	—
Mitral valve	+	+	—
Pulmonary valve ..	+	+	—
Tricuspid valve ..	+	+	+ (Type II)
Throat	—	—	+ (Type II)
Myocardium	—	+	—

All four heart valves yielded a culture of a γ type non-haemolytic streptococcus, and the mitral and tricuspid valves yielded an α type non-haemolytic streptococcus in addition. The blood was sterile.

Case VI

A girl aged 7 had an attack of tonsillitis followed by joint pains a week later. She was then admitted to hospital, where pericarditis developed. Her illness lasted eight weeks in all and she died of heart failure.

A post-mortem examination disclosed an acute rheumatic pericarditis with much fibrinous exudate and free fluid. Acute rheumatic vegetations were present on all valves.

Pathological Findings

	Naked Eye	Microscopical	Growth of Haemolytic Streptococci
Pericardium	+	+	—
Aortic valve	+	+	—
Mitral valve	+	+	—
Pulmonary valve ..	+	+	—
Tricuspid valve ..	+	+	—

Case VII

The patient, a girl aged 5, was admitted to hospital because she was listless, easily tired, losing weight, and had developed swelling of her feet, legs, and abdomen. She gave a history of "growing pains" during the four preceding months. She was found to have an enlarged heart and a mitral systolic murmur. She died a month after admission.

At necropsy slight acute pericarditis and acute endocarditis of all valves except the pulmonary were present.

Pathological Findings

	Naked Eye	Microscopical	Growth of Haemo-lytic Streptococci
Pericardium	+	+	—
Aortic valve	+	+	—
Mitral valve	+	+	—
Pulmonary valve ..	—	—	—
Tricuspid valve ..	+	+	—

The blood was apparently sterile, yet the aortic, mitral, and tricuspid valves yielded growths of both α and γ type streptococci. The other tissues were sterile.

Case VIII

A woman aged 34 was admitted to hospital as a case of hyperthyroidism. She developed tonsillitis, followed a month later by acute rheumatism with precordial pain and pericardial friction. This was treated with intramuscular injections of streptococcal antitoxin, but she died three days later of heart failure.

Pathological Findings

	Naked Eye	Microscopical	Growth of Haemo-lytic Streptococci
Pericardium	+	+	—
Aortic valve	—	—	—
Mitral valve	—	—	—
Pulmonary valve ..	—	—	—
Tricuspid valve ..	—	—	—
Myocardium	—	+	—

Case IX

This patient, a boy aged 10, was healthy until seven months before admission to hospital. He developed flitting joint pains while in bed suffering from fracture of the clavicle. Choreiform movements appeared, and he was admitted to hospital, where he died after two weeks. During his period of hospital treatment he was afebrile.

Necropsy showed that old rheumatic mitral and aortic endocarditis with early mitral stenosis and incompetence were present with recent acute endocarditis of mitral and aortic valves, but there were no lesions of pulmonary or tricuspid valves or pericardium.

Pathological Findings

	Naked Eye	Microscopical	Growth of Haemo-lytic Streptococci
Pericardium	—	—	—
Aortic valve	+	+	—
Mitral valve	+	+	—
Pulmonary valve ..	—	—	—
Tricuspid valve ..	—	—	—
Myocardium	—	+	—

Blood and other tissues were sterile. A pneumococcus, Type IV, was isolated from the mitral valve.

Case X

This patient, aged 15, had rheumatic fever with cardiac involvement for three years, and tonsillitis for two weeks, before coming to hospital. The day previous to admission pericarditis was diagnosed, with precordial pain and friction rub. He was febrile till death, two weeks later. Collapse of lower lobe of left lung developed two days before death, and Stokes-Adams attacks appeared the day he died.

Necropsy revealed an old aortic and mitral endocarditis with acute lesions superimposed. Pulmonary and tricuspid valves were healthy. Acute sero-fibrinous pericarditis and acute pleurisy were present.

Pathological Findings

	Naked Eye	Microscopical	Growth of Haemo-lytic Streptococci
Pericardium	+	+	—
Aortic valve	+	+	—
Mitral valve	+	+	—
Pulmonary valve ..	—	—	—
Tricuspid valve ..	—	—	—
Myocardium	—	+	—

Coliform bacilli were isolated from all tissues, as well as the blood, and in addition an α streptococcus was isolated from the aortic, tricuspid, and pulmonary valves.

Control Necropsies

Ten control necropsies were carried out in the same way as for the cases of rheumatic fever. From none was a haemolytic streptococcus isolated, but from a heart valve in three cases there was obtained an α type streptococcus which was not isolated from the blood.

Discussion

In this series of 10 cases of rheumatic fever a haemolytic streptococcus was isolated from 5. Successful culture was made from 11 valves out of a total of 26 showing acute lesions. This work supports the claims of Green (1939) and Collis (1939).

Death from rheumatic fever in the early acute stage is rare. It is only in valves showing acute lesions and before reparatory processes have been established that the isolation of the infecting organism can reasonably be anticipated. It must be realized that the condition of many cases examined post mortem is such that negative results are likely to be obtained, as many will have survived the early acute phase. Technical difficulties are also encountered, and of these the most important is the presence of other bacteria, especially coliform bacilli, which gain access to the blood either soon after death or in the agonal stage. These bacteria rapidly overgrow the haemolytic streptococcus. For the above reasons the isolation of the causative agent cannot be expected in every case. It is not surprising, therefore, that we were unable to isolate a haemolytic streptococcus from the heart in more than 50% of the cases.

In considering these results two possibilities must be envisaged: first, that haemolytic streptococci are the cause of rheumatic fever and are responsible for the valvulitis by an actual infection of the valve; secondly, that some other process leads to pathological changes in the valves which allow all organisms of various types, including haemolytic streptococci, to lodge there.

In favour of the first hypothesis is the mass of clinical and bacteriological evidence that infection of the upper respiratory tract by haemolytic streptococci precedes and accompanies the syndrome of rheumatic fever. In addition, the finding of Green (1939), Collis (1939), and ourselves that haemolytic streptococci can be isolated from the damaged heart valves of patients dying from rheumatic fever, but not from the undamaged valves of these patients or from the healthy valves of control cases provides strong evidence of this hypothesis. The usual absence of haemolytic streptococci from the blood and their presence in the damaged valve would appear to support this view. It could be argued, however, that the absence of organisms from the blood and healthy tissues was due to the bactericidal effect of blood and tissue reactions, defences which are absent in the avascular vegetations of acute rheumatism.

In favour of the second hypothesis is the fact that the pathological reactions in the valves and myocardium are not those generally accepted as being typical of streptococcal infections. To overcome this difficulty it has been suggested that the patient suffering from rheumatic fever reacts in an abnormal way to streptococcal infection. The joint lesions (which we always found to be sterile) are difficult to explain in terms of an acute infection in view of their fleeting character. If the first hypothesis is correct we would expect that rheumatic valvulitis would develop into malignant endocarditis in the acute or sub-acute stage of rheumatic fever in a considerable proportion of cases, whereas this result occurs only rarely.

Another argument in favour of the second hypothesis is that other types of streptococci were isolated from heart valves and tissues of cases of rheumatic fever and controls where the blood yielded no such organism. Thus an α streptococcus was isolated from 6 damaged valves and from 2 undamaged valves. A γ streptococcus was isolated from 7 damaged valves. An α streptococcus was isolated from 3 valves of the control series. A pneumococcus, Type IV, was isolated from a damaged valve and an α streptococcus was isolated from the spleen of one of the rheumatic series.

It is obviously dangerous to make dogmatic claims in favour of one type of organism when several have been isolated under identical circumstances. It will be noted, however, that a haemolytic streptococcus was isolated only from damaged valves and never from undamaged valves. Haemolytic streptococci can often be isolated from the blood of cases of scarlet fever if repeated blood cultures are examined, and this slight bacteraemia probably occurs in ordinary streptococcal tonsillitis, including that which accompanies rheumatic fever. The point at issue is whether or not the isolation of haemolytic streptococci from valves damaged by acute rheumatism represents an actual infection in the valve or a lodgment in the avascular vegetation following a slight bacteraemia.

The fact that the haemolytic streptococci isolated from throat, blood, valves, myocardium, and brain of any one case were all of the same type (Griffith) would at first appear as strong evidence in support of an actual infection in the rheumatic lesions, but it might be argued that this merely indicates that a blood spread has occurred from the throat. This can be accepted as an argument in favour of either hypothesis, since the results can be interpreted as either a true infection of the tissues or a lodgment of the organism in tissues previously damaged by the rheumatic process.

In conclusion we would say that although at the present time the aetiology of rheumatic fever cannot be said to be solved, we are inclined to support the view that the cardiac lesions are in fact due to infection with haemolytic streptococci.

Summary

Haemolytic streptococci were isolated from the hearts of 5 of 10 patients dying of acute rheumatism and never from controls.

Haemolytic streptococci were isolated from damaged valves, but not from undamaged valves.

Other types of streptococci were isolated from both damaged and undamaged valves, but more often from the former.

The significance of these findings is discussed.

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HYPERVENTILATION AND THE EFFORT SYNDROME

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A syndrome is a number of symptoms frequently observed in combination. "Syndrome" is a descriptive term, and is generally used to avoid premature aetiological conceptions. It may ultimately prove to imply a common aetiology or a common mechanism. More often, however, one finds a limited number of causes liable to produce a syndrome—the typical phrase being, "X syndrome may be due to (a), (b), or (c)." Lewis (1940) applies the term "effort syndrome" to the following group of symptoms: Breathlessness, pain (precordial), exhaustion, giddiness, and fainting; palpitation, headache, and lassitude are additional symptoms of less consequence. This symptom-group "is to be found in a variety of pathological states—for example, in early heart disease, in early phthisis, and in exophthalmic goitre. But it is also found, and in much greater frequency, in soldiers in whom no physical signs of structural changes are discovered."

Among those who show no signs of structural disease a post-infective group stands out clearly; the remainder are classified by Lewis into the constitutionally weak (nervous or physical) and an exhaustive group. The aetiology of effort syndrome is still a puzzle so far as the purely "functional" cases are concerned. Because of the present interest in psychosomatic medicine it is to be expected that the "neurotic" group will attract much attention; and, indeed, no observer with some experience in psychiatric cases will fail to see the similarity between effort syndrome and an anxiety state. This similarity has led to a closer analysis of the symptoms and to an attempt to study effort syndrome by a method which has proved useful in elucidating some manifestations of anxiety—namely, the production of symptoms by voluntary hyperventilation.

Symptoms of Hyperventilation

When a normal person overbreathes sufficiently he will produce two sets of symptoms—(a) a tetanic type, and (b) some disturbance of consciousness. Tingling in the fingertips (or in the toes or lips), numbness of the extremities, stiffness, and a tendency to characteristic postures (*main d'accoucheur*) up to fully developed tetanic spasms, belong to the former group; the description of the symptoms of the latter group varies not only with their intensity but

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