Clinicopathological Conference

Four Cases of Rickettsial Endocarditis

DEMONSTRATED AT THE ROYAL POSTGRADUATE MEDICAL SCHOOL

Clinical Histories

Mr. I. M. BRECKENRIDGE (1): The first patient (Case No. 303121) was a young man aged 25 years at the time of his discharge in 1967. He gave no history of rheumatic fever and had been well until the age of 19, when he had three syncopal attacks on exertion. A heart murmur was first heard two years later, and the patient subsequently developed mild exertional dyspnoea.

On examination he was in sinus rhythm with a blood pressure of 120/80 mm. Hg and the murmurs of aortic stenosis and incompetence. There was no evidence of cardiac failure. The E.C.G. showed left ventricular hypertrophy, and a chest *x*-ray revealed calcification of the aortic valve.

These findings were confirmed on cardiac catheterization, when the pressure in the left ventricle was 180/15 mm. Hg, in the aorta 108/85 mm. Hg, and in the right ventricle 32/4 mm. Hg. In view of the risk of sudden death, an operation was advised and undertaken by Mr. W. P. Cleland on 13 July 1966. Through a median sternotomy, with cardiopulmonary bypass for 170 min., the aorta was opened and the coronary arteries perfused. The aortic valve was functionally bicuspid with only a rudimentary commissure between right coronary and noncoronary cusps. The two coronary cusps were calcified and rigid, and a large boss of calcification occupied the commissure between them. These two cusps were excised and the valve reconstructed, using a strip of fascia lata from the patient's thigh in the manner described by Senning,[1] restoring competence without stenosis.

After operation the patient remained well for four months but then developed all the symptoms and signs of florid subacute bacterial endocarditis, with recurrence of severe aortic incompetence. *Staphylococcus albus* sensitive to a wide range of antibiotics was isolated on two occasions, but a six-weeks course of penicillin, streptomycin, and cloxacillin produced no improvement. The patient was therefore readmitted to Hammersmith Hospital on 10 March 1967, and in the absence of Mr. Cleland a second operation was performed by Professor H. H. Bentall on 3 May.

Extensive vascular adhesions with gross dilatation of the aortic root were noted, and on opening the aorta some destruction of the fascial valve was found. In particular, the left coronary and noncoronary cusps had become detached posteriorly from the aortic ring, and at this point of detachment an opening in the aortic wall about 2 cm. in diameter led into a large false aneurysm lying in the transverse sinus. This aneurysm was some 10 cm. in diameter but did not communicate with any cardiac chamber.

The remains of the fascial valve were excised and the opening of the aneurysm closed by a Dacron patch. A size 12 Starr–Edwards caged-ball valve was then used to replace the defective aortic valve.

Two days after this operation reports of complement fixation tests for *Rickettsia burneti* in the blood, taken a month previously, became available and showed a raised titre. Microscopy of the excised valve disclosed typical rickettsial microcolonies, and *R. burneti* was isolated after guinea-pig inoculation.

Though the patient was febrile for two weeks after operation, and was treated with chloramphenicol, penicillin, streptomycin, and tetracycline, he recovered and was discharged on 31 May 1967 with no evidence of aortic valve dysfunction.

Further Cases

Mr. A. H. DE BONO: I will briefly present three further cases of aortic valve disease coming to surgery associated with infection with *R. burneti*.

Case 2, a man aged 57, was admitted to the Central Middlesex Hospital in February 1966 with severe aortic regurgitation and congestive failure, high sedimentation rate, and raised gamma-globulins. He was given medical treatment but relapsed after a month and was readmitted in April. He had angina, finger-clubbing, and splenomegaly, and was treated as for subacute bacterial endocarditis with 30 mega units of penicillin daily for 14 days with no great change. He was then transferred to Hammersmith Hospital with severe aortic regurgitation. The bone marrow showed increased plasma cells and atypical monocytes. The blood showed an *R. burneti* complement fixation phase I<10, phase II 1/60.

On 19 December 1966 Professor Bentall operated, replacing the calcified aortic valve, which showed vegetations, with a Starr–Edwards prosthesis. Postoperatively the patient was treated with tetracycline, kanamycin, and methicillin.

Case 3, a boy aged 15, had had symptoms of severe aortic stenosis for the last five years, with recurrent febrile episodes and anaemia. Preoperative screening showed a very high titre against *R. burneti*.

Professor Bentall operated on 25 April 1967 and found that the aortic cusps were thickened and showed a number of vegetations. There was marked subaortic fibromuscular obstruction, which was relieved by wedge resection. The post-operative treatment was with penicillin, kanamycin, and tetracycline.

Case 4, a man aged 45, had a congenital cardiac lesion which was symptomless until 1963, when he began to have bouts of dyspnoea, pyrexia, and congestive failure with splenomegaly, raised sedimentation rate (60 mm./hr.), and raised gamma-globulins. He was treated with penicillin. On his admission to Hammersmith Hospital in 1965 all agglutination tests and blood cultures were negative. The aortogram showed a ruptured sinus of Valsalva. Raised gammaglobulins (especially gamma M = 1,600 mg./100 ml.) were present.

At operation on 16 May 1967 Mr. Cleland found a ruptured right coronary cusp. The right ventricle showed a small aorto-pulmonary window and perforation of the other aortic cusps. The aorto-pulmonary window was made good with a Teflon patch and the valve was replaced by a Starr–Edwards prosthesis. The excised cusps showed *R. burneti* on section. Post-operatively the patient was treated with tetracycline. The *R. burneti* complement fixation titre in 1966 was 1/280. The patient received further tetracycline.

These three cases illustrate the presentation of this type of infective endocarditis, which does not respond to penicillin,

and in which the blood cultures are negative. The diagnosis is clinched by complement fixation tests. They also illustrate the role of surgery in the treatment of severe aortic regurgitation and pose the problem of whether to replace the damaged cusps with an inert prosthesis or a homograft valve in the presence of active infection. It was considered that the inert prosthesis was structurally more reliable, and that a homograft may be exposed to destruction by the infection.

Pathological Findings

Dr. E. G. J. OLSEN (3): CASE 1: The specimen consisted of three pieces: (1) a single aortic valve cusp (3 × 2.3 cm.) (Fig. 1). A suture line 1 cm. from the lower thickened portion was seen, and the valve was hard and showed irregular whitish areas. Small granular areas were also present. (2) A smaller valve cusp (2.7 × 1 cm.) showing a slight thickening but no other changes. (3) Consisted predominantly of Teflon.

Histology.—Sections of the previously repaired valve cusps showed a well-healed scar and an occasional focus of foreign-body giant cells around some suture material. The granular area consisted of rounded bodies of mottled tissue under the ordinary haematoxylin and eosin stains, but on special staining (Macchiavello) these showed definite microcolonies of *R. burneti* (Fig. 2). These microcolonies measured about 40 to 80 microns in diameter. The organisms stained red with the Macchiavello stains and took on a blue-mauve colour with Giemsa. A diagnosis of rickettsial endocarditis was made.

CASE 2: The specimen consisted of pieces of aortic valves, the largest measuring about 2 × 1.5 cm. The valves were irregularly thickened, the thickest portion measuring up to 3 mm. In two of the three recognizable cusps perforations were present, each showing at the margins white thickening.

Histology.—Histological examination of the specimen showed complete destruction of the normal architecture of the valve cusps, calcification, and fibroelastic thickening with hyaline change. Many microcolonies of organisms having the staining reaction for rickettsiae were present (Fig. 3).

CASE 3: The specimen consisted of a portion of heavily calcified aortic valve. A commissure was seen, and though fusion had occurred this was placed below the superior ends of the commissures. The thickness of the valve cusps varied between 1.5 mm. at the base and 3.5 mm. at the free edge. Along the free edge there were a number of rounded excrescences.

Histology.—Histological examination of the section of the valve showed some retention of normal architecture in a few areas. Most of it, however, showed a gross thickening consisting of hyaline and fibroelastic tissue. A few foci of inflammatory cells were present as well as many large foci of calcification. The valve was examined by frozen section and electronmicroscopy and special staining. None of these showed any evidence of rickettsiae.

CASE 4: The specimen consisted of two pieces of brownish-grey tissue, each measuring about 3 × 7 mm.

Histology.—All of the pieces consisted entirely of fibroelastic tissue arranged in a very irregular pattern. The second piece of tissue showed hypertrophied myocardium with fine patchy fibrosis. The endocardium for the most part was incomplete, but in one area it was thickened. A small focus of fibrosis with some inflammatory cells scattered among it was also found. Special staining failed to reveal any rickettsiae.

Epidemiology and Chemotherapy of Q Fever

Dr. J. H. DARRELL (4): In most, and probably all, cases Q fever endocarditis follows from an acute attack 6 to 18 months previously.

The acute condition was described first by Derrick[2] in 1937, after it had been found in slaughterhousemen in Brisbane, Queensland. The "Q," however, stands for "Query" and not Queensland, as has sometimes been said. Soon afterwards Burnet and Freeman[3] described the causal rickettsia, now more correctly called *Coxiella burneti.*

It has since been amply confirmed[4] that animals form the principal natural reservoir of the disease, though how man acquires infection from this reservoir is still rather obscure. In this country cattle, sheep, and goats are infected, the organism localizing particularly in the placenta and milk of pregnant animals. Large numbers of organisms are then shed at parturition. The fact that they resist drying particularly well and have been isolated from the dust from clothing of farm workers, together with the fact that the vast majority of cases of acute Q fever present as acute pulmonary infections, makes it likely that infection in man is by inhalation of contaminated dust.

The patient described in Case 1 was a tractor-driver from Scotland, and the last published case of Q fever endocarditis also occurred in a Scottish tractor-driver. Here at least there is a clear connexion with rural communities and farming, but this is not always so. He also admitted to drinking raw milk. Marmion,[5] who did much of the important early work on this condition, was unable to decide whether milk was an important vehicle of infection. In spite of the fact that rickettsiae may readily be isolated from it, it seemed unlikely that they would survive passage through the stomach.

Turning to the serological diagnosis of the condition, we have heard references today to results of complement fixation tests in this and other patients. It is important to note that two types of antibody (phase I and phase II antibodies) are detectable in Q fever. The terms refer to the antigen used in testing. Phase II antibodies occur in all infections with *C. burneti,* acute or chronic. They are detected with an antigen made from the yolk-sac of the hen's egg using a strain of coxiella fully habituated to growth in this site. In the first few passages in eggs freshly isolated strains grow less readily, but the material can be used to detect the other antibody (phase I), the presence of which is restricted to chronic Q fever. With one exception (Case 2) all the patients referred to today had phase I as well as phase II antibodies. The patient in Case 1 had titres of 2,560 (phase I) and 1,280 (phase II). Phase I antibodies at this high titre strongly suggest the presence of endocarditis. Other forms of chronic Q fever may occur, but here the titres are usually lower—little over 100. Like all laboratory tests this one is not infallible. One of the cases mentioned today as being suggestive of Q fever endocarditis (Case 2) had phase II antibodies only, and Marmion[6] reported a case, confirmed at necropsy by the demonstration of organisms in sections of heart valve and by isolation of the rickettsiae, in which phase II antibodies only were present, and these were at quite a low titre (64). There was a reference to the fact that when first examined the serum of the patient in Case 4 was reported to be negative. This was due to a prozone phenomenon, not previously known to affect this test, which caused a negative reaction in the lower serum dilutions up to 1 in 400. Re-examination showed a titre of 1 in 10,240 with phase I antibodies also present.

Choice of Antibiotics

The final aspect of the condition I intend to discuss is the choice of antibiotics used in treatment. I must take issue with one speaker about *Staphylococcus albus* not being a recognized pathogen in endocarditis. When it is isolated from a minority of cultures the rest of which are sterile, as in this patient, one should retain a healthy scepticism about the significance

of this organism, but it certainly can cause endocarditis, particularly after cardiac surgery.

On his readmission here it was felt that, even in the absence of positive bacteriology, the fever and the patient's (Case 1) general condition demanded antibiotic treatment prior to the further surgery which he undoubtedly needed. I was not entirely responsible for his initial treatment with benzylpenicillin, cephaloridine, and kanamycin, but in the circumstances, though this is blunderbuss therapy, it is probably one of the best and most logical combinations that could have been used.

In infective endocarditis of undiagnosed aetiology a penicillin (either benzylpenicillin or one of the semisynthetic penicillins), together with a streptomycin-like drug, of which kanamycin is probably the best, is the most effective combination. They are bactericidal drugs and are likely to show synergy at least against the gram-positive cocci. In this case benzylpenicillin with cephaloridine combines the most active of the penicillins with an analogue effective against penicillinase-producing organisms.

When, as a result of the serological investigations, the diagnosis of Q fever endocarditis was made in this patient the combined therapy was changed in favour of chloramphenicol. The intention was to substitute tetracycline for long-term treatment after a short course of chloramphenicol.

Here I should say that while these drugs are indicated in Q fever endocarditis their effect is by no means ideal. They are only rickettsiostatic, not cidal, and cure with antibiotics alone is unlikely and has probably never been achieved in this condition. They are, however, capable of halting the progress of the infection for long periods provided irreparable damage has not already occurred to a valve. The penicillins and streptomycin are inactive against rickettsia. I doubt whether any of us knows what kanamycin does against this organism, but as its action is very similar to that of streptomycin one would not perhaps expect it to be very active. None the less, just prior to reoperation, after three weeks' treatment with penicillin and kanamycin, the patient was afebrile, and certainly the clinical impression was that he had been improved by this antibiotic combination. If it could be proved to be effective in this condition it would, being bactericidal, hold out a better chance of cure. We hope, with the co-operation of the Central Public Health Laboratory, Colindale, to test the action of kanamycin against coxiella grown in eggs.

It was rather alarming that when the change to the so-called specific antirickettsial drugs was made immediately postoperatively the patient's fever recurred. This corresponded with an episode of clinical wound infection and soon settled. When the further change to tetracycline was made there was again a brief rise in temperature associated with bacteraemia due to Enterobacter. Before the organism was identified penicillin and streptomycin were again added to the tetracycline treatment. The organism was sensitive to both tetracycline and streptomycin, and the fever quickly settled. The patient was discharged on long-term tetracycline therapy.

Finally, I should say that in addition to the serological and histological evidence of rickettsial infection the Virus Reference Laboratory was able to isolate *C. burneti* from egg inoculum from the remnants of the fascia lata graft excised at the second operation.

Serum Protein Changes in Rickettsial Endocarditis

Dr. J. HOBBS (5) : The cardiac surgeon is often faced with the clinical problem of a patient with fever, signs of carditis, and a raised serum level of γ-globulin. In the absence of other diseases affecting the γ-globulin level, the probable causes are bacterial endocarditis, nonbacterial endocarditis, and postcardiotomy syndrome. In recent years it has become possible to measure serum immunoglobulins and assess the contribution of the known classes (γG, γA, γM, and γD) to the observed raised γ-globulin. This approach has sometimes been helpful not only to the diagnostician but also towards our understanding of the functions of the different immunoglobulins.

Present knowledge suggests that the 7S γG-globulin is formed largely in response to soluble antigens, such as toxins, and that the main function of such antibodies, which circulate freely throughout the body fluids (60% are extravascular), is to inactivate any soluble products that might diffuse from foci of infection. The γA globulin is mainly 7S in the serum, and most seems to be secreted into the respiratory and alimentary tracts in an 11S form not susceptible to our digestive enzymes. In the colostrum such antibodies seem to protect the suckling's gut. It is known that γM-antibodies are best formed in response to particulate antigens and appear before γG in some natural diseases—though this may only reflect an early bloodborne phase. It is far more efficient than γG at fixing complement and destroying cell surfaces (1 molecule γM is worth 7,000 of γG) and seems to be the best antibody for killing bacteria or foreign cells. However, because of its 19S size 80% remains intravascular. To be effective in the tissues, etc., it would have to be made on the spot. Little is known of γD, which accounts for <1% of the total daily production.

Fig. 4 summarizes the Hammersmith results together with additional Q fever material from Drs. R. G. Sommerville and D. A. McSwiggan.[7] Bacterial endocarditis results in a fairly equal increase in all three immunoglobulins, a pattern seen in over 100 other patients with bacterial infections.

Rickettsial endocarditis shows a predominantly γM response, which is maintained for months while the disease is active. This is similar to the response seen in patients with malaria, trypanosomiasis, and bartonellosis. All are characterized by living organisms continuously within the blood-stream. In ordinary Q fever, without an obvious infection of the blood, the immunoglobulin response is much less ; indeed, γG and γA are lacking (a single serum complement fixation test can show a much higher and diagnostic titre if the heart is affected.) Thus it is not just the particulate nature of the rickettsial antigens but their continued intravascular presentation that evokes the massive γM response. This γM has sometimes had cold agglutinin activity, so that sera should be separated at 37° C. The low-output cardiac failure and peripheral cooling could explain the gangrene of the ears originally described in the *B.M.J.* by Ball[8] in what was later shown to be the first British case of rickettsial endocarditis. Even 17 years ago emboli were not considered the cause. The markedly raised γM levels may, however, reflect the length of time prior to diagnosis (average four months). Treatment with tetracycline abolishes the fever and lowers the γM. Patients with bacterial endocarditis may fail to achieve such γM levels either because they are diagnosed and treated earlier (average one month) or because the disease is more rapidly fatal. We have no experience of long-continued intravascular bacteria and do not know if this could give the same γM picture.

In patients in whom postcardiotomy syndrome was finally diagnosed the response was only in γG. This has been a typical early and helpful difference in many autoimmune disorders.

Finally, besides the association of blood-stream infection with a γM response, foreign red cells provoke γM agglutinins, and we have observed that of 29 patients with idiopathic γM-deficiency no fewer than 10 have suffered proved septicaemia. The neonate with little γM allows *Escherichia coli* to spread through the blood to the meninges. Thus, while immunoglobulin measurements may have only a limited application in rickettsial infections they have helped to define the normal function of γM, which I believe is to protect the bloodstream, while γG looks after the body fluids and γA the gut and respiratory tract.

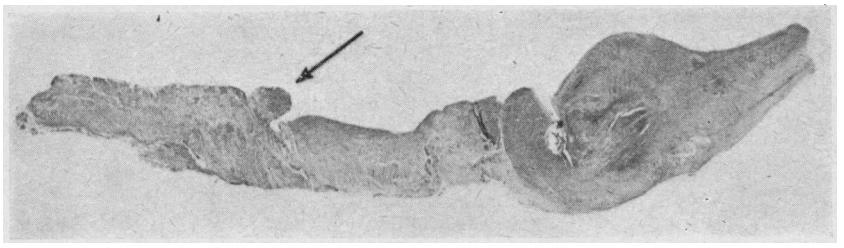

FIG. 1 —Aortic valve cusp. On the right of the specimen the thickened, distorted aortic valve cusp is seen. The thinner tissue is the extension by fascia lata. The arrow points to a small vegetation. (Weigert's elastic van Gieson. ×6.3.)

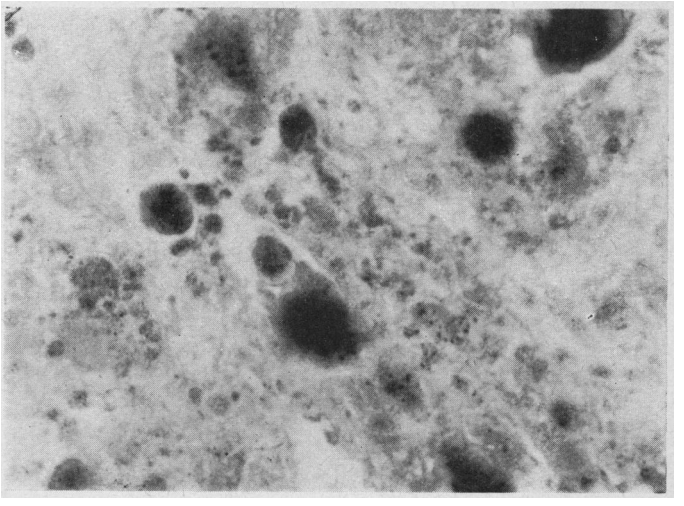

FIG. 2.—High-power view of vegetation. The dark areas are microcysts containing the organisms which appear as small dots within the cysts. (Case 1.) (Macchiavello. ×800.)

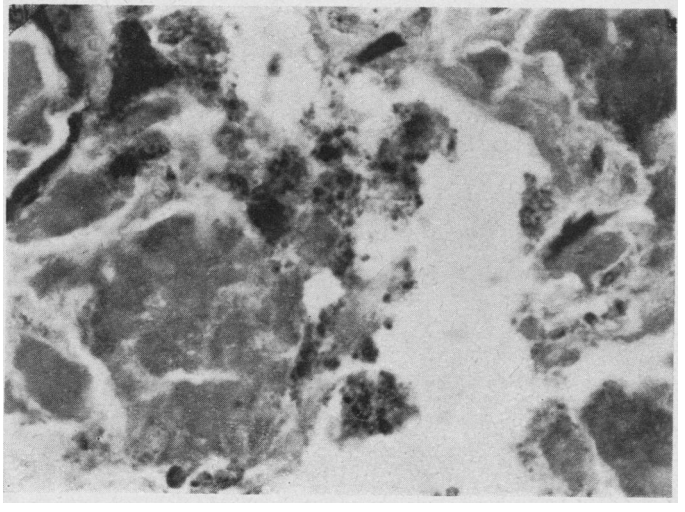

FIG. 3.—High-power view of valve cusp showing microcysts and numerous rickettsia, which are the smaller dots. (Case 2.) (Giemsa. ×800.)

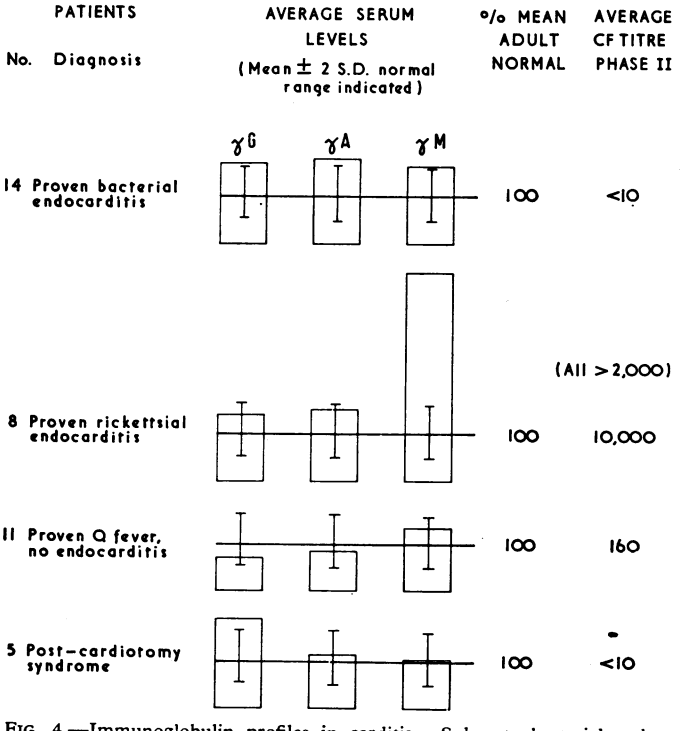

FIG. 4.—Immunoglobulin profiles in carditis. Subacute bacterial endocarditis shows an all-round increase in immunoglobulin levels, rickettsial endocarditis a predominantly γM response, and postcardiotomy syndrome mainly γG.

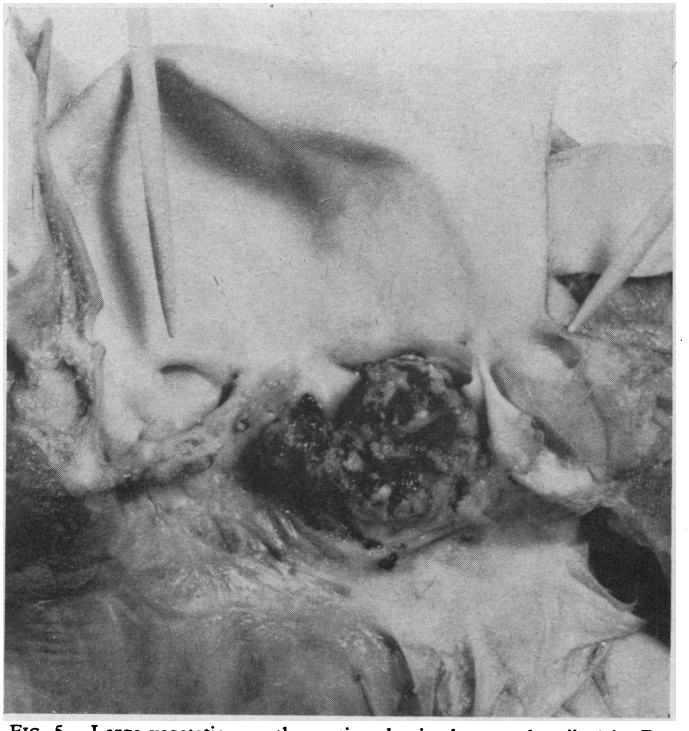

FIG. 5.—Large vegetation on the aortic valve in the case described by Dr. R. J. Harrison.

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Discussion

Mr. BRECKENRIDGE: Before throwing this subject open for general discussion there are two people I should like to call upon. The first is Dr. R. J. Harrison, who is here today and who has details of the first case of rickettsial endocarditis, which he described in this hospital, and Dr. C. M. Oakley, will, I think, speak from the medical point of view.

Dr. R. J. HARRISON (6): That patient first attended hospital in 1959. Her presenting symptoms were due to coronary embolism from the vegetation on the aortic valve (Fig. 5). Some weeks later the destructive endocarditis caused incompetence of this valve.

Repeated blood cultures were negative, and there was no evidence of the source or occasion of her infection. She was born and bred in London, had never been into the country, and had had no contact with animals.

In the course of her work in a hotel cloakroom she met travellers from many parts of the world, handling their clothing and laundry, and the possibility of Q fever endocarditis was considered. Her serum was sent to Dr. Marmion for serological tests, and he reported complement-fixing antibodies to both antigenic phases of *C. burneti*. The organism was also isolated from blood cultures.

C. burneti is remarkably resistant to heat, drying, and chemical disinfectants, and the principal route of infection in humans is thought to be by inhalation from contaminated aerosols or dusts. Probably the most concentrated natural source of *C. burneti* is tick faeces.

Ticks are important reservoirs and efficient vectors for distributing this organism among their host animals. Inhalation of contaminated dusts from infected clothing was one possible source of infection in this instance.

Turning now to this morning's Case 1. There was no evidence of infection at the first operation in July 1966, and a possible source of his *C. burneti* infection might have been the transfused blood he had received.

Mr. BRECKENRIDGE: Perhaps Dr. Oakley could now guide us back to the initial problem of the aortic valve—a simple disease to our surgical minds.

Dr. C. OAKLEY (7): I think the ground has been covered so very well that I will only ask a few questions to which I haven't yet found the answer. First of all, a plea concerning the patient suspected of infective endocarditis. I wonder, when we have eliminated those persons who have had a short course of antibiotics which has sterilized their bloodstream, and the patients with rheumatic endocarditis or other sorts of non-infective endocarditis, how many of the only too common remaining patients really have rickettsial endocarditis? How common is it? We have ourselves only recently taken to looking for rickettsial antibodies routinely. Secondly, I wonder whether chloramphenicol was a good choice for the post-operative treatment of our patient. Not only is it only rickettsiostatic rather than rickettsicidal, but I am told that it is one of the poorest penetrators of cells, and is therefore unlikely to reach these intracellular organisms.

Next, the patient in Case 2, who appeared to be pretty firmly diagnosed and had a very high antibody titre indeed, showed no evidence of rickettsiae in his valve at operation: one wonders whether the tetracycline had cured him. If so, he would be the first patient who had been cured of rickettsial endocarditis as far as I know.

The third point is that Dr. Darrell mentioned a period of latency of 6 to 12 months. What grounds does he have for saying this? We weren't able to pinpoint any overt respiratory illness followed by a long pause. I wonder how anybody has been able to ascertain this period of latency, and, if there is one, what is thought to be the reason for the latent period being so long after an acute respiratory infection.

With relevance to the patient in Case 1, may I mention a familiar bone of contention? He was sent home on "prophylactic" penicillin. Prophylactic against what? He had congenital heart disease, not rheumatic, and there was no reason to give him penicillin on his discharge. I just wondered if when he got a respiratory infection it would make him more prone to get an infection with unusual organisms. He was in a farming community, and perhaps this rendered him a little more liable to be infected with a rickettsial organism.

Mr. BRECKENRIDGE: He stopped taking the penicillin, so that question did not arise, but the other questions are very firmly directed to you, Dr. Darrell. What answers have you?

Dr. DARRELL: Can I deal with the period of latency first? The most recent publication by Marmion[6] mentions seven proved and two possible cases of endocarditis. In the seven proved cases he found that in every one there was an episode which was clinically suggestive of acute Q fever, and he mentions that the interval beween this episode and the first diagnosis of endocarditis was between 6 and 16 months.

Dr. HOBBS: If I may chip in there, the final diagnosis was made at two, three, six, eight, and nine months respectively in five of our patients,[7] but this refers to the months from the onset of symptoms of infective endocarditis, not to any previous interval.

Dr. DARRELL: I am sorry. I didn't mean to imply a period of latency before endocarditis supervened, merely between the diagnosis of this and the acute episode, which I think is almost invariably present.

Which Antibiotic?

On the other issue—"the question of chloramphenicol and tetracycline"—these are the only two drugs possible. This organism is an intracellular parasite, and I think neither of these two drugs gets into the cell very easily—which is probably why they are so ineffective as antirickettsial agents, as they suppress rather than eradicate the infection. Has anyone else any comments for or against chloramphenicol and tetracycline? Some people give chloramphenicol as being possibly more active initially and then carry on with the less toxic tetracycline as long-term therapy. I don't think one would choose tetracyclines for their greater penetrating value.

Dr. OLSEN: Dr. Oakley also asked one question on incidence. Going through the literature, I think Marmion and his colleagues[9] in 1960 gave some indication. They investigated 56 cases of infective endocarditis, but only one of the 56 had the antibodies associated with healed Q fever endocarditis, so it would appear that numerically the incidence is low.

Professor J. E. GOODWIN (8): Can I ask a question? My impression was that the patient had no infection at the time of the first operation, which might bear on the question of transmission through transfusion.

Mr. BRECKENRIDGE: His original disease was purely congenital, and at operation nothing was found to suggest infection.

Dr. OAKLEY: Don't you think he got the infection when he went home, because surely the γM in the bloodstream which Dr. Hobbs told us about should prevent successful transmission through transfusion?

Professor GOODWIN: Yes, I should think he got it at home. Another point, perhaps, is that although this disease seems to affect mainly the aortic valve, it does occasionally affect the mitral valve, and I was interested to see a patient from Devon referred to me recently with a history and a clinical picture very like that of left atrial myxoma but with very high titres for rickettsiae. The doctor who made the diagnosis and referred the patient said he had an exactly similar patient a year or two before: I think these people were farmers.

Dr. Kristinsson has made a study of the published cases of rickettsial endocarditis, and perhaps he would like to add something.

Dr. A. KRISTINSSON (9): Ten cases (all fatal) of Q fever endocarditis have been published in the English literature. Nine of them died from haemodynamic causes and one after a mitral valvotomy. All had some previous valve lesion, and it seems likely that infection occurs only if there is some previous abnormality.

Regarding Dr. Oakley's question on the patient in Case 2, I wish to support the diagnosis of Q fever endocarditis. The diagnosis was made five months before his operation. He was treated for two months with tetracycline and was apparently cured, because after the operation his valve was subjected to careful examination by both light- and electron-microscopy, immunofluorescence, and injection tests into guinea-pigs. All were negative, but still the history and the clinical course were very strongly suggestive of Q fever endocarditis.

Dr. HOBBS: Furthermore, during this period of treatment he reduced his antibody from 1/4,000 to 1/128, and his γM from 320% to 90% of normal: so by the time of operation something had been done.

Professor H. H. BENTALL (10): The clinically interesting thing about him is that at the time of operation the edge of his valve had been eroded in a way which I have never seen with bacterial endocarditis. There was a very curious nibbled-up effect as though a rat had been gnawing the edge of the valve—quite unlike the sort of punched-out holes one sees with bacterial endocarditis.

Dr. HOBBS: Apropos the other point that Dr. Darrell made about kanamycin. Case 1 had the lowest result—1/1,000 (all the others have had values of over 1/2,000)—in the complement fixation tests, and he also had a γM which was only just above normal. So the idea that kanamycin may have done him some good may be a correct one.

Surgical Aspects

Mr. BRECKENRIDGE: To cover aspects of the cases other than Q fever, I should like to ask the question about the use of fascia lata for a valve reconstruction. How should one replace the valve when there is a suspicion, or indeed evidence, that the bloodstream is infected by any organism? These are perhaps important points.

Mr. W. P. CLELAND (11): The question of which method of repair to use is a very important surgical point. In bacterial endocarditis homografts have been used successfully and have stood up to the test of time over quite a long period, but the position may be different with the rickettsial bodies. On the evidence that we've got so far it would look as though natural tissues ought to be avoided if you've got a positive diagnosis.

Professor BENTALL: I believe that in one case of Q fever (from South Africa, I think) in which an aortic valve was replaced with a homograft, the patient subsequently died from the total dissolution of the homograft. I haven't been able to verify this statement.

Dr. OLSEN: May I ask Dr. Darrell something on morphological appearance? One reads in textbooks on bacteriology that the rickettsiae are intracellular. Now, in all the sections that we looked at here, the organisms are always in little cysts up to about 80μ across, as I've shown you. Sometimes one finds only four or six of these organisms, but one never really finds them in any recognizable cells. What is the possible explanation for that? Is it that we see them when they are already dead, or is it that it is the chronicity or the chemotherapy that had an influence on the morphological appearance?

Dr. DARRELL: The suggestion is that what you're looking at in these sections is microcolonies. These arise from single organisms and build up. In fact, having presumably originated in a macrophage, by the time the colony has reached this size you're not really seeing what is left of the original cell. Also, if it is not too insulting, may I suggest that sometimes in the processing of the tissues something which might have been originally intracellular might have arrived outside it?

Dr. OLSEN: Yes, that has been explained[10] as being due to the disappearance and degeneration of nuclear and cytoplasmic sections. But even so, one should still see some sort of nuclear material and cell remnants despite even the most injurious processing in producing a slide. I realize that these were microcolonies, but I meant that even if there are a small number of organisms only they are never seen inside a cell.

Mr. DE BONO: On the same subject, may I ask whether this could have any possible bearing on the amount of M globulin, and whether the rickettsiae are intra- or extracellular?

Dr. HOBBS: I don't know. I would think the reason the blood cultures are negative is that the antibody present in the blood-stream makes sure of this, and I think the only way of getting positive cultures is from the valve itself.

Mr. DE BONO: No, but what I meant was that if there is an exposed antigen it is more likely to stimulate antibody production, and a different type of cell may be producing it. One other point: there were comments on atypical monocytes or lymphocytes, and I don't know if anyone could enlarge on that. Are these antibody-producing cells?

Mr. BRECKENRIDGE: I think we are reaching the limits of people's knowledge, so this might be a suitable point to draw the proceedings to a conclusion. We are very grateful to all speakers for their contributions, and I have certainly found this very interesting and educational. I only hope that everybody else has. Thank you very much.

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The appointments held by the speakers at the conference are listed below:

(1) Mr. I. M. Breckenridge, Senior Registrar, Department of Surgery.
(2) Mr. A. H. De Bono, Lecturer, Department of Surgery.
(3) Dr. E. J. G. Olsen, Lecturer, Department of Morbid Anatomy.
(4) Dr. J. H. Darrell, Lecturer, Department of Clinical Bacteriology.
(5) Dr. J. R. Hobbs, Lecturer, Department of Chemical Pathology.
(6) Dr. R. J. Harrison, Consultant Physician, St. James' Hospital, Balham.
(7) Dr. C. M. Oakley, Lecturer, Department of Medicine.
(8) Professor J. F. Goodwin, Professor of Clinical Cardiology.
(9) Dr. A. Kristinsson, Registrar, Department of Medicine.
(10) Professor H. H. Bentall, Professor of Cardiac Surgery.
(11) Mr. W. P. Cleland, Part-time Senior Lecturer, Thoracic Surgery.

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