Clinicopathological Conference

A Case of Resistant Staphylococcal Endocarditis

DEMONSTRATED AT THE POSTGRADUATE MEDICAL SCHOOL OF LONDON

Clinical History

Professor J. F. GOODWIN: The patient (Case No. 291093; P.M. No. 10851) was a Greek who was aged 21 years at the time he was first seen at Hammersmith Hospital. He had been normal in infancy, but a cardiac murmur had been heard at the age of 2 years. Childhood was uneventful and there was no limitation of effort tolerance. In 1960, at the age of 17 years, he suffered an epistaxis, and an infection of the nose followed nasal plugging. As a result of this infection he was febrile, but responded to arbitrary antibiotics. Two months later, in January 1961, the fever recurred and blood cultures grew *Staphylococcus aureus* (coagulase positive). The fever responded to antibiotics and to corticosteroids. A diagnosis of staphylococcal endocarditis complicating congenital aortic stenosis was made.[1] He was treated with novobiocin and erythromycin. The infection relapsed. *Staph. aureus* was again cultured and was found to be sensitive to erythromycin, novobiocin, kanamycin, and methicillin. He was treated with methicillin 6 g. daily, and erythromycin was also given. The fever responded slowly, but blood cultures were again negative. However, the fever recurred again and he suffered a pulmonary embolus. In January 1962 he was readmitted to hospital with a further febrile attack. Blood cultures were again positive for *Staph. aureus* and he was treated with cloxacillin; other penicillins were also given. Between the years 1962 and 1964 there were six relapses of fever and he was in hospital for periods of two to three months at a time. On each occasion the fever responded only temporarily. In March 1964 he was admitted to hospital for the seventh time in severe heart failure, which did not respond to treatment. He was flown to England and was admitted urgently to Hammersmith Hospital on 24 April 1964. At this time the symptoms were those of weight loss, malaise, lethargy, sweating, severe dyspnoea and orthopnoea, and ankle swelling. He had also had some haematuria.

On examination he was orthopnoeic and almost moribund. He was sallow, pale, and emaciated; there was clubbing of the fingers and oedema of the legs. The pulse was regular at 110/min. and the blood-pressure 120/40 mm. Hg. The jugular venous pressure was elevated to 10 cm. above the sternal angle; there was a poor *x* descent, and a large systolic wave indicating tricuspid incompetence. There was massive (grade 4) enlargement of the left ventricle and moderate (grade 2) enlargement of the right ventricle. The arterial pulse was regular, of large volume, and water-hammer in type. All the arterial pulses were present. At the aortic area there was a loud, long ejection murmur followed by a loud, early diastolic murmur. Both these murmurs were also heard at the left sternal edge. At the cardiac apex there was a long systolic murmur, a loud third heart sound, and a mid-diastolic rumbling murmur. Aortic valve closure was faint, and pulmonary valve closure could not be separated from aortic. The lungs showed basal rales. The liver was hard and enlarged to a point six finger-breadths below the costal margin. The spleen was also enlarged and hard, and there was some ascites. The patient was febrile, with a maximum temperature of 100° F. (37.8° C.).

Investigations

The urine contained numerous red blood cells, occasional white cells, hyaline and granular casts, and albumin.

X-ray of the chest showed considerable generalized cardiac enlargement and interstitial pulmonary oedema (Fig. 1).

The electrocardiogram showed grade 3 left ventricular hypertrophy and digitalis effects. The PR interval varied from 0.1 to 0.12 second; the P waves were inverted in lead II, VF,

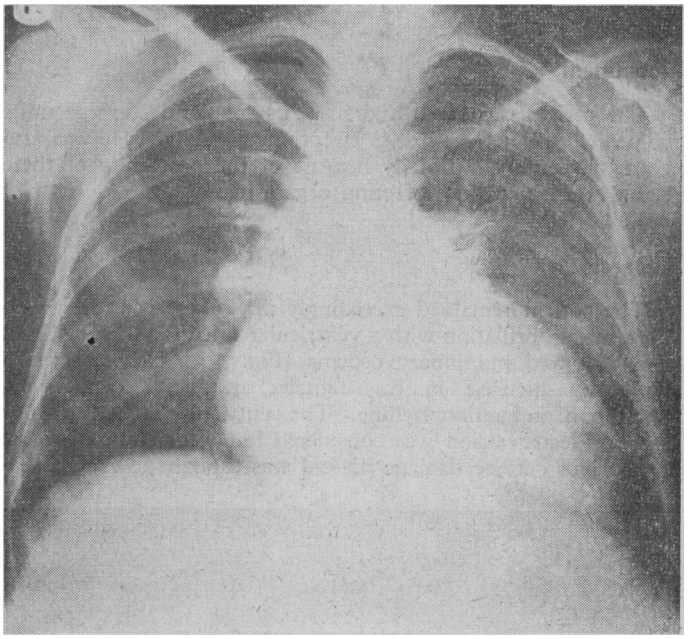

FIG. 1.—6 ft. postero-anterior chest radiograph on 24 April 1964, showing massive cardiac enlargement, mainly of the left ventricle and subacute pulmonary oedema. The aorta and main pulmonary arteries are enlarged, and the right atrium prominent.

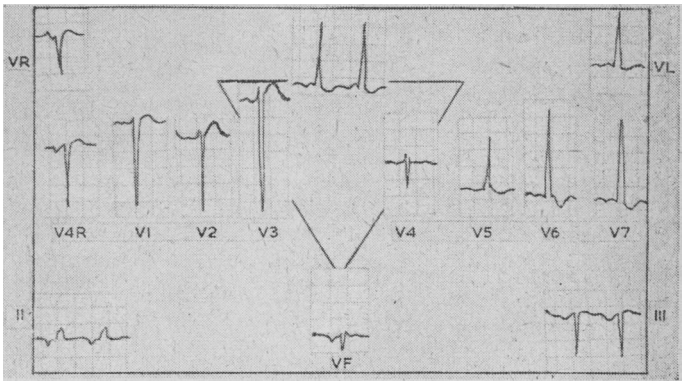

FIG. 2.—Electrocardiogram on 24 April 1964, showing considerable (grade 3) left ventricular hypertrophy, digitalis effects, and high nodal rhythm of coronary sinus type.

and III, and biphasic in lead I, indicating high nodal rhythm of coronary sinus type (Fig. 2).

Clinical Diagnosis

(1) Congenital aortic valve disease, ? bicuspid valve.

(2) Staphylococcal endocarditis, probably active, causing rupture of an aortic cusp.

(3) Left and right ventricular failure.

(4) Possibly mitral incompetence.

(5) ? Embolic nephritis.

Further Investigations

E.S.R. was 90 mm./hr. Serum sodium was 136 mN, and potassium 4 mN. Blood urea was 74 mg./100 ml., haemoglobin 11.3 g./100 ml., and white cell count 10,000/c.mm. Reticulocytes were 5.4%. Serum bilirubin was 0.9 mg./100 ml. Alkaline phosphatase was 90 King-Armstrong units, thymol turbidity 3 units, and zinc sulphate 8 units. Serum albumin was 2.5 g./100 ml., and globulin 4.5 g./100 ml.

Blood cultures (Figs. 3, 4, and 5): In all, 20 venous and arterial blood specimens and one bone-marrow specimen were examined. All grew *Staph. albus* of coagulase-positive type.

Treatment

The patient was given digitalis, diuretics, and 20 mega units of penicillin daily, with 1 g. streptomycin daily. He was also given cloxacillin 2 g. daily because of the possibility of there being more than one infecting organism.

Progress

The patient remained exceedingly ill. On 6 May he developed atrial fibrillation with a ventricular rate of 140/min. Chest *x*-ray showed pulmonary oedema (Fig. 6). He was treated with an increase in his digitalis and with pronethalol, Omnopon, and aminophylline. The ventricular rate fell to 100/min. Electroversion was considered but was rejected because the serious cardiac damage present was thought to render success improbable. He remained critically ill and on 7 May developed cardiac arrest due to ventricular asystole. He was treated by external cardiac massage, isoprenaline, adrenaline, and sodium bicarbonate. Ventricular fibrillation then developed. External D.C. defibrillation resulted in a return to sinus rhythm, which was followed by atrial fibrillation. By this time he was unconscious and was put on intermittent positive-pressure respiration. Blood electrolytes at this time were: potassium 5.2 mN, sodium 140 mN, and bicarbonate 34.3. The blood *p*H was 7.39, and the arterial oxygen 95% saturation. Despite these measures he developed cardiac arrest at 1 p.m. and died.

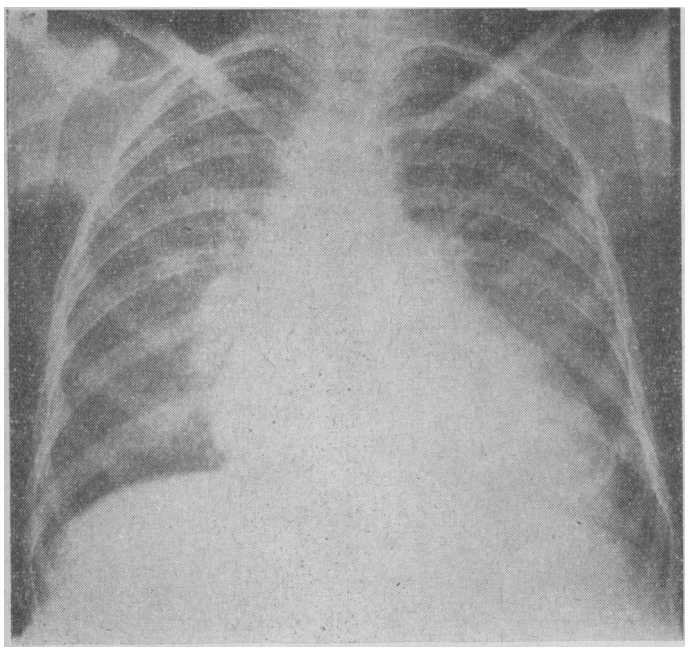

FIG. 6.—6 ft. postero-anterior chest radiograph on 6 May 1964, showing pulmonary oedema.

The final diagnosis was therefore congenital aortic valve disease, active staphylococcal endocarditis producing aortic incompetence (probably due to a ruptured cusp), and possibly mitral valve infection also. Congestive heart failure and left ventricular failure, tricuspid incompetence, and possibly embolic nephritis were complications.

Post-mortem Findings

Professor C. V. HARRISON: The patient was a rather thin young man, 5 ft. 4½ in. (1.6 m.) in height and 7 st. 4 lb. (46.3 kg.) in weight.

The *heart* weighed 850 g. (normal 310 g.). The pericardium was obliterated by old fibrosis. The left ventricle was greatly hypertrophied but only moderately dilated. Just below the aortic valve (Fig. 7), on the ventricular septum, was a string-like cord of fibrosis parallel with the valve and causing a sub-aortic stenosis. Microscopically (Fig. 8) this proved to be a cord of fibrous tissue 3 mm. wide and 4 mm. deep and was presumably congenital. There was infective endocarditis of the aortic valve. The right coronary cusp was thickened by fibrosis but free from endocarditis. The non-coronary cusp (Fig. 9) was ulcerated and only tags of cusp and vegetations remained. The left coronary cusp was involved by endocarditis, but most of the actual cusp was present. Above the non-coronary cusp there was an irregular plaque of intimal fibrosis on the aorta, quite distinct from atheromatous fibrosis and presumably infective in origin (Fig. 10). The mitral valve (Fig. 11) showed infective endocarditis of the middle of the anterior cusp but without ulceration. There was no continuity between the aortic and mitral endocarditis. The rest of the mitral valve was moderately thickened by fibrosis. It had a normal formation of papillary muscles and chordae, but these were covered by a layer of endocardial fibrosis. Microscopically the mitral (Figs. 12 and 13) and aortic valves showed infective endocarditis with masses of cocci, mostly Gram-negative but with a few giving Gram-positive staining. Cultures were negative, suggesting that these cocci were all dead. The fibrosis of the posterior mitral cusp was confirmed.

The right ventricle was hypertrophied; the tricuspid and pulmonary valves were normal. The coronaries were normal. There were small foci of fibrosis in the left ventricle. Nowhere was there any evidence of rheumatic carditis.

The *lungs* were heavy; the right weighed 1,250 g. (normal 450 g.) and the left 1,010 g. (normal 400 g.). This was partly due to passive congestion but mainly to oedema. No infarcts or infarct scars were found. Both pleurae were obliterated by old adhesions. Microscopically the passive congestion was confirmed and several medium-sized pulmonary arteries showed old intimal fibrosis of a type suggesting healed pulmonary emboli.

The *liver*, 2,225 g. (normal 1,500 g.), and *spleen*, 748 g. (normal 160 g.), showed the changes of chronic venous congestion. The spleen and kidneys showed small infarct scars.

The *kidneys* were enlarged, weighing 695 g. together (normal 300 g.). Macroscopically there was no abnormality apart from the signs of passive congestion. Microscopically there was a

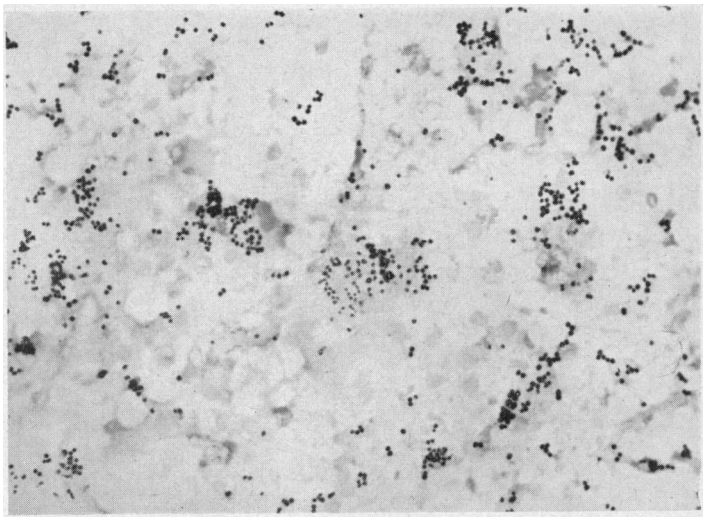

FIG. 3.—Gram-stained film from blood-culture bottle showing many poorly stained ghost-like cocci and swollen cells.

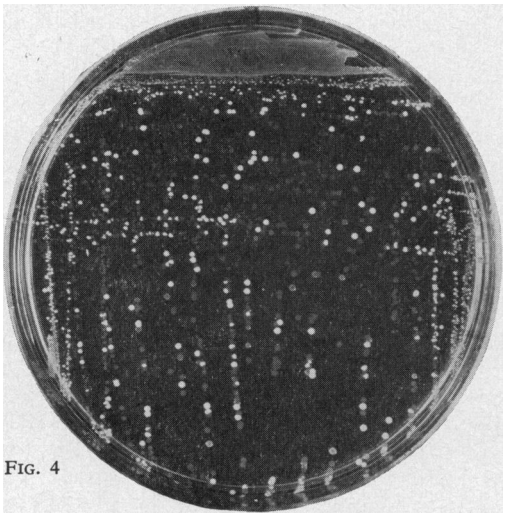

FIG. 4

FIGS. 4 and 5.—Early subcultures on blood agar showing colonies of varying size and opacity.

FIG. 7. — Heart showing aortic valve. The left coronary (right) and non-coronary cusps are partly destroyed by endocarditis. Below and left of the right coronary cusp (left) is a white bar of fibrous tissue that caused subaortic stenosis. Above the infected valves the aorta shows irregular intimal thickening.

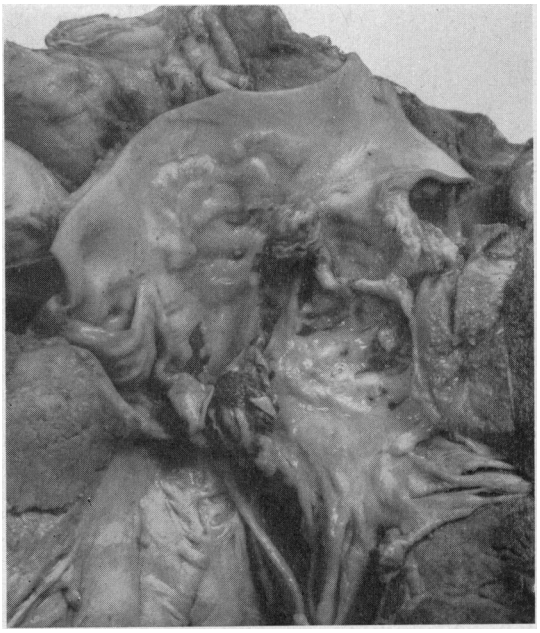

FIG. 7

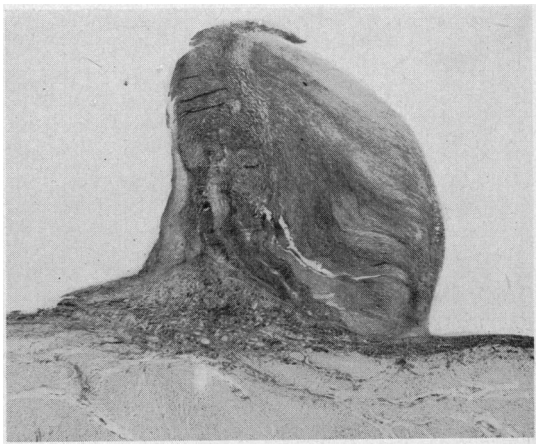

FIG. 8.—Section across the subaortic stenosis showing a bar of dense fibrosis. (Elastic van Gieson. ×12.)

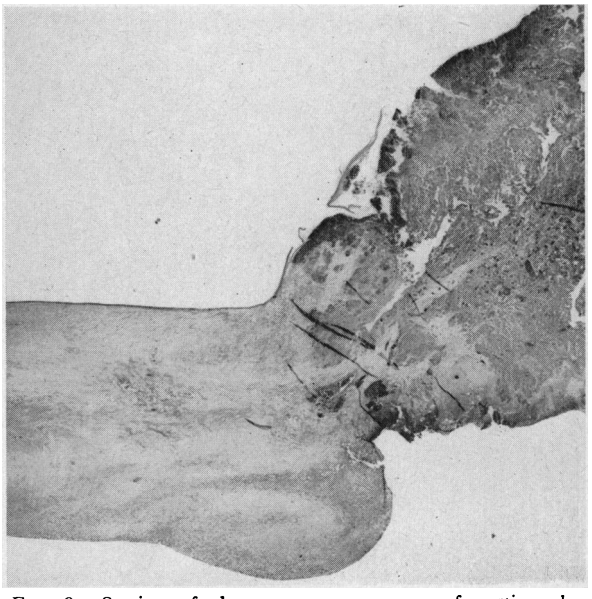

FIG. 9.—Section of the non-coronary cusp of aortic valve showing a vegetation. (H. and E. ×13.5.)

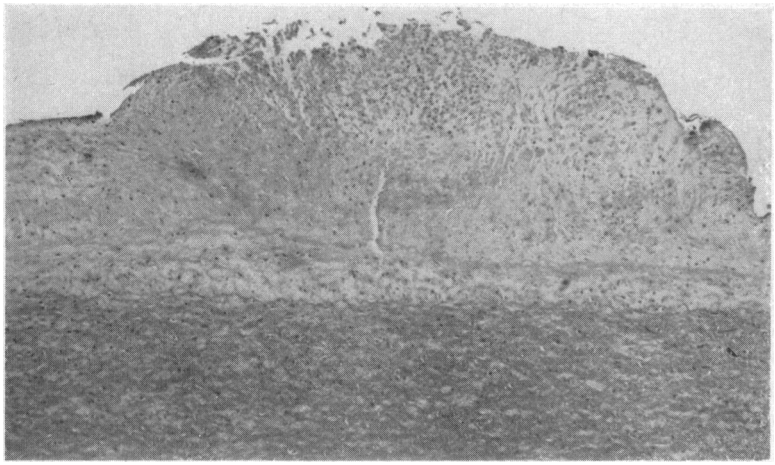

FIG. 10

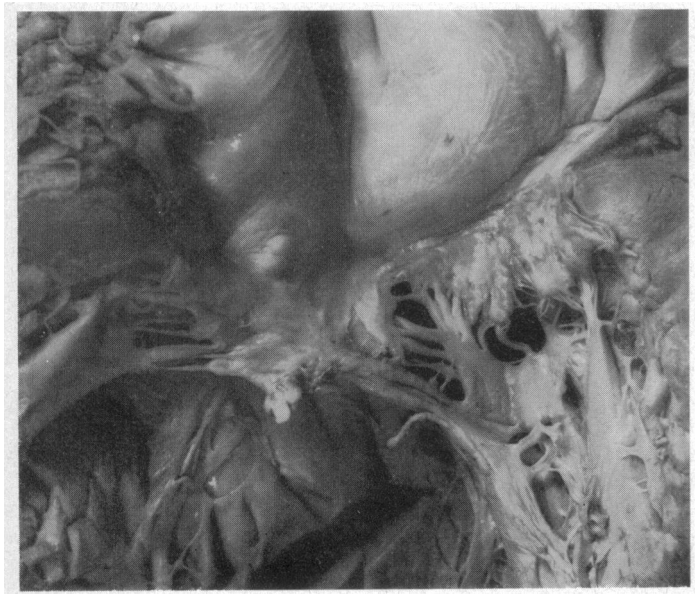

FIG. 11

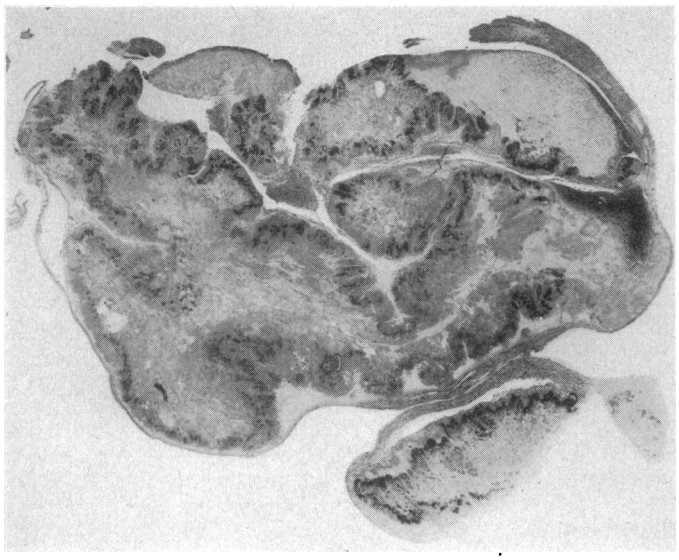

FIG. 12

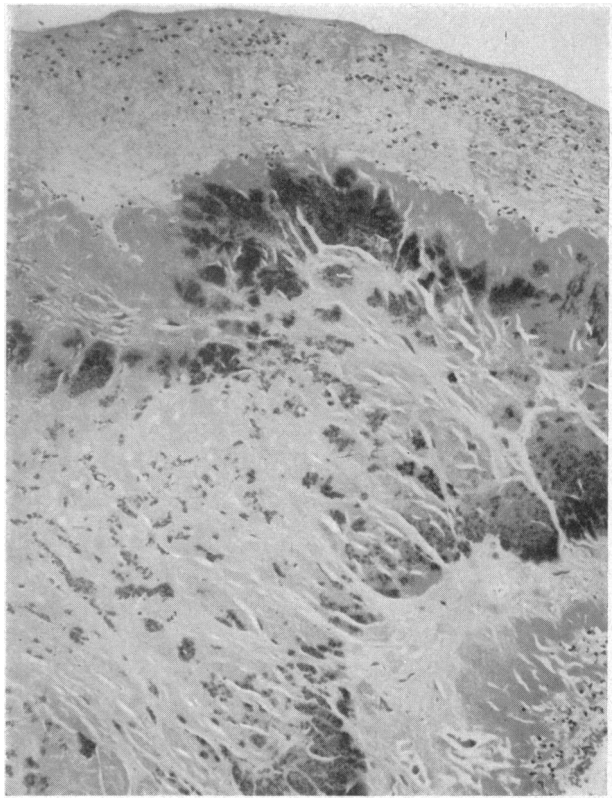

FIG. 13

FIG. 10.—Section of aorta showing an inflammatory endocarditis. (H. and E. ×60.)

FIG. 11.—Mitral valve. At the edge of the aortic cusp is a pale vegetation.

FIG. 12.—Section of vegetation on mitral valve shown in Fig. 11. (H. and E. ×12.)

FIG. 13.—High power of Fig. 12 showing fibrous tissue, colonies of cocci (dark), and very few inflammatory cells. (H. and E. ×100.)

FIG. 14.—Glomerulus showing lobing, fibrosis, and, on lower left, a crescent. (Mallory's stain. ×260.)

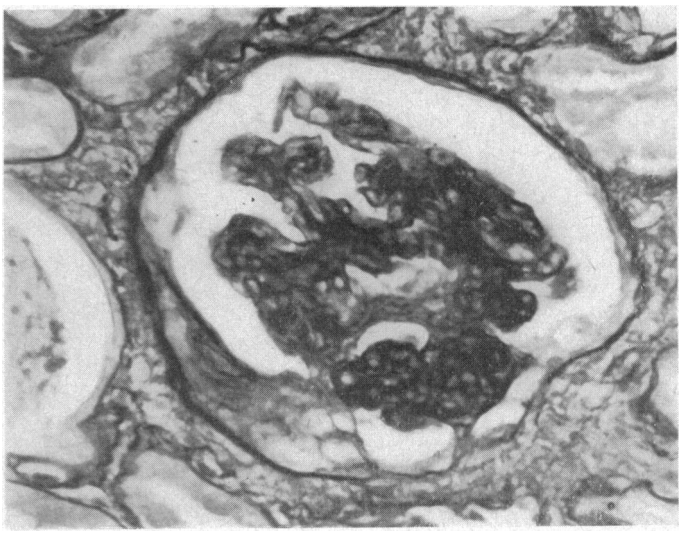

FIG. 14

glomerulonephritis (Fig. 14). A few glomeruli showed capsular adhesions and crescents. They all showed lobing and fibrous thickening with diminution of the capillary lumina and thickening of the capillary walls. They were appreciably enlarged. The tubules showed the signs of proteinuria, but there was scarcely any tubular destruction. The appearances were those of an intra-capillary glomerulonephritis and not of focal embolic nephritis.

Other organs were within normal limits.

Pathologist's Diagnosis

(1) Congenital subaortic stenosis due to a fibrous band.

(2) Infective endocarditis with gross destruction of aortic valve cusps and infective endocarditis of aortic cusp of mitral valve. The endocarditis was sterilized and heart failure was due to valve destruction.

(3) Passive venous congestion of lungs, liver, spleen, and kidneys.

(4) Infarct scars in spleen and kidneys.

(5) Massive oedema of lungs.

(6) Subacute glomerulonephritis.

Discussion

Professor MARY BARBER*: This patient is not only a very interesting case but proved to be a very difficult one. We had considerable difficulty in diagnosing precisely what the organism was. As Professor Goodwin has pointed out, we had 20 blood cultures, no fewer than ten on a single day, so that I think we can congratulate the clinicians on their desire to get a positive bacteriological diagnosis in a case of endocarditis, the importance of which I have emphasized at many of these conferences. Perhaps I should add that some members of the Bacteriology Department thought that ten in one day was a little excessive, but in the event I think they proved useful.

Appearance of Staphylococcus

Our report in the first blood culture was *Staph. albus* and micrococci in one bottle only. When we use the term *Staph. albus* without qualification we mean a coagulase-negative organism, and indeed in initial tests this appeared to be a coagulase-negative staphylococcus; the term "micrococci" I am afraid we use rather loosely to mean cocci that have not got quite the arrangement of the staphylococci and usually have smaller colonies. Organisms of this sort are very common serial contaminants; so on blood culture 1 we might have been prepared to shrug our shoulders and say that these organisms in one bottle only didn't mean very much. In the next blood culture *Staph. albus* was isolated from one bottle and in the next one gave no growth at all. Thereafter we variously reported *Staph. albus* in one, two, or three bottles, or micrococci. Subsequent studies have shown that all the organisms isolated were the same species, which was in fact a strain of *Staph. aureus* giving rise to various morphological and cultural appearances.

Fig. 3 is a Gram stain taken from one of the blood-culture bottles—you can see that we have some very large darkly staining cells, some moderate-sized ones that might have done for staphylococci, and some that are simply ghosts. Since this is in fact a single organism, it is not surprising, perhaps, that we had difficulty in diagnosing it. Fig. 4 shows a culture plate. Again there is a variety of different types—some colonies look like *Staph. albus* while others are almost completely transparent. Fig. 5 shows a culture at a higher magnification, and it will be seen that the colonies are of many different sizes; only the large colonies are typical of staphylococci. The small colonies resemble cultures sometimes isolated from patients who have had osteomyelitis for perhaps five to ten years; these are often referred to as G forms. A paper in the *Journal of Infectious Diseases*[2] suggested that they represented a kind of "spore" form of the staphylococcus that turned up under unfavourable conditions. These dwarf colonies were shown to have a non-specific resistance to all sorts of antiseptic agents. I myself isolated one such colony from a patient with osteomyelitis which resisted boiling.

Initially the cultures isolated from this patient gave a number of different antibiotic sensitivity patterns, presumably due to non-specific resistance. Once they had been subcultured a few times they tended to revert to more typical staphylococci and were weakly coagulase-positive; some even produced an aureous pigment. The sensitivity pattern also became constant and they were consistently resistant to benzylpenicillin. They were sensitive to most other antibiotics that were tested, except that they showed a very slight degree of resistance to methicillin.

Plan of Antibiotic Treatment

The other thing I want to talk about is the antibiotic treatment, because that was a little complicated too. The following antibiotics are all active against staphylococci: *benzylpenicillin, methicillin* and *cloxacillin,* fucidin, novobiocin, erythromycin, lincomycin, and *vancomycin.* I have emphasized those which are highly bactericidal because, as I am sure you are aware, in the treatment of endocarditis it is important, if possible, to treat with a bactericidal agent. Now first of all, if you have a staphylococcus which is sensitive to it there is nothing to touch good old-fashioned benzylpenicillin: it is far and away the most active antibiotic for a penicillin-sensitive staphylococcus. Next I put down methicillin and cloxacillin, two of the new penicillins which are resistant to staphylococcal penicillinase. Penicillin in some form or other is nearly always the best drug for staphylococcal infection. Then, to be up to date, I put down cephaloridine, which Glaxo have marketed under the trade name Ceporin. This is a bactericidal agent which will attack penicillin-resistant staphylococci. Next I have put down vancomycin, although I think there are people in this room who will think that this is an extraordinary thing to do, because vancomycin is a very toxic drug and is very liable to cause deafness. But in my opinion it is one of the most active anti-staphylococcal drugs we have, and I think it is something to keep in the back of one's mind for a very difficult case. Fucidin, erythromycin, novobiocin, and lincomycin are all fairly active anti-staphylococcal agents, but with the possible exception of fucidin they are not actively bactericidal. Moreover, with these antibiotics the problem of resistance is great unless they are in various combinations.

Antibiotics Given to this Patient

Now let us see what the patient had. First of all in Greece he had novobiocin and erythromycin—quite a good cover for staphylococci but not a really bactericidal treatment and so not ideal for endocarditis. The response was temporary, as would be expected. In July 1961 methicillin was given. This at first had a very good effect, but after about three weeks the temperature spiked again, and after continuing methicillin alone for a few days erythromycin was added. Now this in my opinion was bad treatment, because erythromycin, which is bacteriostatic, frequently antagonizes the bactericidal action of the penicillins. The patient then became an out-patient, and here the story is not very clear. While out of hospital, various combinations of tetracycline, benzylpenicillin, and Aminosidin were given. I think the latter antibiotic is a Pharmitalia product which resembles neomycin. If this is so it is a bactericidal agent which might be synergistic with penicillin, but the addition of the bacteriostatic antibiotic tetracycline was a

* Professor Mary Barber died on 11 September 1965. (See *B.M.J.*, 18 September, p. 707.)

mistake. Then the patient went back to hospital in 1962 and was treated with oxacillin. This is cloxacillin with one chlorine atom missing, and its anti-staphylococcal action is similar. Then the patient was given Cillocycline. I think this is a Pharmaceutici-midy (Milan) compound which is a mixture of tetracycline and benzylpenicillin. If so, this was a bad compound to use, since tetracycline antagonizes the bactericidal action of penicillin. But of course the clinicians were getting desperate with a patient who was not responding to the usual treatment. Finally he was given benzylpenicillin and streptomycin.

Then the patient came here. Because of the difficulty of diagnosing the organism in the blood culture, and because of the previous difficulties in finding effective drugs, we decided to give the widest possible bactericidal cover. He was given benzylpenicillin in very large doses plus streptomycin and cloxacillin. One of the things at the back of my mind is whether vancomycin might have helped, but I think it is probably true to say that eradication of bacteria at this stage was not likely to save the patient's life. At post mortem the heart vegetations were sterile, although I believe Professor Harrison showed that organisms were still present in films.

Sensitivity of Organisms

Dr. J. P. SHILLINGFORD: What were the sensitivities of these organisms to the various drugs ?

Professor BARBER: Although tests were difficult on primary isolation the infecting staphylococci were consistently resistant to benzylpenicillin. They were sensitive to streptomycin, tetracycline, chloramphenicol, erythromycin, novobiocin, neomycin, and kanamycin. They were doubtfully sensitive to methicillin.

Dr. SHILLINGFORD: If they were resistant to benzylpenicillin, for what reason did you prescribe the drug ?

Professor BARBER: Well the resistance to benzylpenicillin is simply caused by the production of penicillinase. With such strains the individual cells are sensitive to benzylpenicillin, but a large inoculum inactivates the antibiotic. If multiplication of the organism is prevented—for example, with cloxacillin—then the benzylpenicillin can take effect. A combination of benzylpenicillin with a penicillinase-resistant penicillin may even have a synergistic effect.

Professor GOODWIN: I think actually we put him on these before we consulted you.

Dr. SHILLINGFORD: So *in vitro* resistance tests may not always be entirely helpful ?

Professor BARBER: Exceedingly helpful to clinicians now that we have so many drugs. If the only drug we had was benzylpenicillin, it wouldn't matter if it was resistant or not, you would have to treat with benzylpenicillin but give larger doses ; however, clearly benzylpenicillin was not the drug of choice for this type of organism. Of course, penicillinase production is a special case. With all other drugs resistance is a drug tolerance, and the organism will continue to grow in the presence of increased concentration of the antibiotic.

Professor RUSSELL FRASER: Perhaps in practice " resistance " is not entirely a black-and-white affair ?

Professor BARBER: That's true. With the staphylococcus it is very difficult to give a figure for resistance, because it depends so much on the size of inoculum. However, as Professor Goodwin knows, with *Streptococcus viridans* and *Str. faecalis* endocarditis we give the minimum inhibitory concentration of each drug by itself and with two drugs together. That way we can choose what is the most effective combination.

Professor GOODWIN: I think this discussion emphasizes the importance of early consultation between clinician and the bacteriologist when faced with this type of problem.

Professor BARBER: That is important. If we do sensitivity tests without ever meeting the clinicians our reports may be totally meaningless ; we may be choosing an arbitrary level of sensitivity which is the wrong level for the treatment.

Chronicity of Endocarditis

Professor GOODWIN: It is now clear that bacterial endocarditis can go on for years. We discussed this possibility on a recent occasion, and this patient proves the point, but what is surprising is that it can go on for so long in such a virulent form. Presumably it might go on for even longer in a less virulent form. In patients with heart disease one should think of the possibility of bacterial endocarditis lasting for a very much longer period than one tended to think before. I think this patient was exceptionally unlucky, and his doctors in Greece were faced with an unusually difficult problem, in that he got this resistant and very treacherous organism from his original nasal infection. This case underlines the extreme importance of treating even an apparently trivial infection rigorously in a patient with known heart disease. Without being too wise after the event we can perhaps say that if the organism had been tracked down more carefully right at the beginning and more appropriate antibiotics given the situation that followed might not have arisen. The course of the disease needs no further comment ; it is fairly typical except for the duration.

Cardiac Lesions

The cardiac lesions are very interesting. In young people we reckon that we can nearly always tell at the bedside the difference between congenital *discrete subaortic* stenosis, which is usually a fibromuscular band or bar below the aortic valve, and *true valve stenosis*. In valvar stenosis there is a systolic click, aortic valve closure is well heard unless the valve is calcified, and often there is a trivial aortic diastolic murmur. In *discrete subvalvar* stenosis there is no click, aortic valve closure is very soft, and there is often quite an appreciable diastolic murmur. But in the presence of gross valve destruction, incompetence, and severe heart failure the distinction may be impossible, and this patient had both valvar and subvalvar stenosis. I was certainly surprised to find subaortic stenosis at necropsy, but I have seen patients with both forms of stenosis, and obviously infection can occur on subvalvar as well as valvar obstruction. It is interesting, if I read the pathology right, that the bar itself seems not to have been affected, but in some way perhaps deflected the organism on to the valve—although I suppose it is very possible that the valve was initially abnormal also. One cannot tell what the valve had been like originally, it was so extensively destroyed.

We were very interested in the possibility of a mitral lesion, since patients with discrete subaortic stenosis often have congenital abnormalities of the mitral valve. One of these is the so-called " parachute valve " in which the chordae converge to be inserted into one papillary muscle. This produces a combination of obstruction and incompetence, often in association with subvalvar aortic stenosis, supravalvar ring in the left atrium, and coarctation of the aorta.[3]

Management of Arrhythmia

On the question of management, I probably made a mistake in not advising electrical conversion of his atrial fibrillation. If we could have got him back to sinus rhythm quickly and restored his atrial activity, perhaps he would not have developed his terminal cardiac arrest. But it seems that the cardiac damage was so massive that really nothing would have prolonged his life for very long ; indeed, when I first saw him two weeks before, I thought that he was moribund at that time. We tried very hard to do everything possible to save this patient,

because there was the possibility at the back of our minds that if we could sterilize the infection and get him out of heart failure it might be possible to replace his aortic valve. In this connexion, of course, it is very important to know what the myocardium is like. I should like to ask Professor Harrison if there was any definite myocardial abnormality apart from hypertrophy ; also, was there any evidence of bacterial infection in the myocardium ?

Professor HARRISON: No, there was nothing worse than that little bit of fibrosis which I mentioned.

Professor GOODWIN: Thank you. I think his heart failure was really too severe for electrical conversion of his fibrillation to have been successful, or for surgery to have been contemplated in the presence of infection. But even if the chances of obtaining reversion to sinus rhythm by electrical means are poor it is probably worth trying, because these patients do often desperately need their atrial activity to improve their ventricular function.

Origin of Nephritis

I think the nephritis is very interesting. I don't think I can add anything on that ; perhaps Dr. Wrong can. We thought it was embolic and focal because he had changes in the urine with a "normal" (for his degree of heart failure) blood urea. I have always found diffuse nephritis with bacterial endocarditis without rheumatic activity rather difficult to understand, but I am sure there are people here who understand it very well.

Professor FRASER: Dr. Wrong, would you explain why this patient had nephritis ?

Dr. O. WRONG: A diffuse glomerulonephritis is quite common in bacterial endocarditis. We would describe this one, I suppose, as a mixture of proliferative and membranous glomerulonephritis. I don't know the aetiology.

Professor FRASER: Would anybody like to suggest why this occurs ?

Professor BARBER: Well, I remember a similar case that Dr. Wrong treated. I think the infecting microbe was *Str. faecalis*. Dr. Weinbren, whom I invariably believe, said that it was more common with *Str. viridans*.

Dr. H. K. WEINBREN: According to the morbid anatomical findings patients who die with subacute bacterial endocarditis have both diffuse glomerulonephritis and focal glomerulonephritis, and for many years it was thought that the focal variety was due to small emboli. The fact of the matter is that nobody has ever been able to show the emboli, and this so-called embolic lesion occurs only in subacute bacterial endocarditis that has been going for some time and never in the acute endocarditis when patients die very soon. Therefore, since embolization of other organs occurs in both acute and subacute endocarditis the focal renal lesion is unlikely to be embolic. Because the cases that usually go on for a long time are due to *Str. viridans* people have tended to associate the embolic lesions with *Str. viridans,* but I think the same sort of thing might happen irrespective of what the organism was. The most likely cause is some sort of hypersensitivity reaction.

Professor FRASER: Even if it is a focal case ?

Dr. WEINBREN: Yes. Especially in a focal case.

Possibility of Sensitization

Dr. J. R. HOBBS: Many hypotheses of hypersensitivity have been proposed to explain diffuse glomerulonephritis, a few with good experimental support in animals, but none could be substantiated in the human disease[4] until the recent work on a post-streptococcal nephritis. This disease has two important facets ; first, only certain strains of haemolytic streptococci are involved, and, secondly, only a few of the subjects exposed to known nephritogenic strains get nephritis. Markowitz and Lange[5] have explained this. They have shown that the victim has the same type of antigenic substance in the basement membrane of his glomeruli as that in the wall of the particular streptococcus. He makes antibodies against the streptococcus which unfortunately then cross-react with his own glomeruli. This antigenic accident is better called isoimmune rather than autoimmune disease, and is the basis of the hypersensitivity of acute post-streptococcal glomerulonephritis.

In this patient's staphylococci, or in the *Str. viridans* of subacute endocarditis, there is no known substance identical to human glomerular membrane, so that a different mechanism has to be postulated. Experimental Masugi nephritis follows the injection into rabbits of antigen-antibody complexes ; these are believed to lodge in the glomeruli until a secondary immune reaction occurs with subsequent damage. This might explain the present findings, and in similar post-endocarditis diffuse nephritis the glomeruli could be investigated for gamma-globulin and antigens of the infecting organism, but I know of no such evidence.

Dr. SHILLINGFORD: Dr. Hobbs, do you think that the same thing might possibly happen on the heart valve itself, with sensitization followed by infection ?

Dr. HOBBS: I don't know. I think that this can't be the whole story. When I was a houseman, before the new penicillins came in, I saw four patients die of staphylococcal septicaemia with endocarditis, and in all four patients there was no previous history of any abnormality of the heart valve. I do think, not in this case, but in other cases, staphylococcus can get on what was previously a normal valve.

Professor BARBER: That is well known.

Dr. SHILLINGFORD: I was wondering whether the valve itself could be sensitized with an antigen-antibody reaction.

Professor BARBER: I don't see why it should be. After all, the point about nephritis is that the organism is not necessarily there at all, so that you have got to account for nephritis in the absence of an organism. But in the heart valve the organism is there.

Professor HARRISON: Those of us who are getting pretty ancient will remember doing post mortems on children who died in a few days of acute fulminating osteomyelitis. These children had ulcerative staphylococcal endocarditis on their valves within days. There was no time in these children for sensitivity to develop.

Dr. HOBBS: That is a very good point. Two of our four patients died within five days of septicaemia, when an antigen-antibody reaction could barely have occurred.

Dr. C. C. BOOTH: An Osler's node in the skin does seem to be an embolic accident—you can culture an organism from it. Does that never occur in the kidney in the totally untreated case ?

Professor HARRISON: An Osler's node is something you can see with the naked eye in a piece of tissue that is not particularly vulnerable. I would say that the equivalent in the kidney is a tiny yellow infarction. Now when you talk of the so-called focal embolic lesion you are really thinking of a glomerulus which is a fraction of a millimetre and you are taking a tiny fraction of that again. I think we are talking of two different orders of size.

Dr. WEINBREN: Nobody has ever isolated organisms in the so-called focal embolic nephritis.

Prophylaxis of Endocarditis

Dr. BOOTH: Could I bring up another point for Professor Barber ? If you have a patient with a congenital heart lesion or a rheumatic heart lesion, what antibiotics should one give and what precaution should one take over the course of an illness such as this patient had when he was 17 ?

Professor BARBER: Oh, adequate bactericidal treatment. I imagine that when he had this at the age of 17 they did actually identify the staphylococcus.

Professor GOODWIN: I don't think so. I think the nasal infection was recognized and he was given antibiotics arbitrarily. I fancy the answer to Dr. Booth's question is to get the appropriate blood cultures, and then give the appropriate antibiotics if possible.

Dr. BOOTH: Presumably before you give antibiotics you have a pre-existing lesion. Would you advise long-term antibiotics in the same way as we give them to someone with pyelonephritis ?

Professor BARBER: No, that is not the usual practice. I don't think it is a good idea to treat them for the whole of their life with antibiotics, because then there is a very big chance that eventually they will get endocarditis from some organism that we have no antibiotic for. But one must obviously give them antibiotic cover at certain times—for example, during tooth extraction.

Dr. BOOTH: What does one cover them with ?

Professor BARBER: For a person who has never had endocarditis, for a tooth operation, usually benzylpenicillin, because you are thinking mainly in terms of mouth flora. But if a patient is on benzylpenicillin because he has got endocarditis and you still want to remove the teeth you should probably cover with a different antibiotic, such as vancomycin, because for a short 24-hour period vancomycin is pretty safe. If the patient gets any type of infection, this should clearly be treated with a bactericidal drug if possible, and in very large doses to make quite sure you eradicate any focus of infection.

Indication for Electroversion

Dr. J. P. D. MOUNSEY: May I ask Professor Goodwin about a point that he made ? He said that in retrospect he would have advised early electroversion for rapid restoration of sinus rhythm after the development of atrial fibrillation. Obviously the chances of permanent success were small, because the heart was very much shot to pieces as a result of endocarditis. The fact remains that the actual mode of death was an arrhythmic one. It seems to me that this is a question of interest, because cardioversion is the only possible way in which the patient's life could have been prolonged. I also notice that the patient developed atrial fibrillation within a fortnight of admission. I think I am right in saying that the first electrocardiogram on admission showed abnormal P waves and evidence of coronary sinus rhythm. This would presage the development of a more serious arrhythmia such as atrial fibrillation. May I ask Professor Goodwin how he would now, supposing one were starting again, treat this case from the point of view of management of the serious arrhythmias that developed ?

Professor GOODWIN: The prevention of the onset of serious arrhythmias is really very difficult, because the usual drugs which we have been accustomed to using, such as procainamide and quinidine, are not always effective in preventing arrhythmias, and can be dangerous. The beta-blocking agent pronethalol and its successor propranolol, of which we have had considerable hopes in prophylaxis, especially of dire arrhythmias, is not always effective.[6,7] Often the best thing to do is to prevent the patient getting into electrolyte trouble, particularly low potassium states which tend to trigger off arrhythmias. We would not now give propranolol in this sort of situation, since we realize that it can be dangerous in a patient with heart failure who desperately needs his catecholamine stimulus—which is removed by propranolol. We gave it because we thought there might have been slight digitalis intoxication and would have liked to reinforce the action of digitalis in slowing his ventricular rate or in reverting him to sinus rhythm. We did in fact slow his ventricular rate, but we did not get him back to sinus rhythm. Clearly, in retrospect, I think the most important thing is the control of electrolytes and other factors which might precipitate arrhythmias and in selected patients electroversion if arrhythmia occurs.

However, I don't really think that anything that we did would have made the slightest difference in the end. I brought this question up deliberately because I think it is an important principle which we ought to consider earlier in the treatment of arrhythmias.

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