

processes to write their own story and taught his pupils how to interpret the records. His work laid the foundations of modern methods of experimental study of the problems of the circulation.

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(To be concluded)

BACTERIAL ENDOCARDITIS: POSSIBILITY OF CURE BY SULPHONAMIDES

WITH REPORT OF A CASE

BY

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The endocardium is one of the latest territories to be assailed in the chemotherapeutic advance of the last few years. It was inevitable, however, that drugs which had been used with such marked success in bacterial invasion of other tissues should be applied to the treatment of the corresponding infection of the endocardium. The reports so far available are on the whole encouraging (Ellis, 1938; Whitby, 1938a, 1938b; Manson-Bahr, 1938; Major and Leger, 1938).

In attempting to assess the possible value of any chemical agent in the treatment of this malady certain factors have to be constantly borne in mind. (1) The difficulty that exists in certain cases in establishing the diagnosis. (2) The possibility of spontaneous recovery. (3) The anatomical peculiarities of the site of infection and of the lesion, which render the organisms difficult to reach by therapeutic agents.

The Diagnostic Difficulty

The cardinal signs of bacterial endocarditis are usually given under four heads (Horder, 1920, 1926): (a) multiple arterial embolism; (b) evidence of existence of endocarditis; (c) presence of bacteria in the blood stream; (d) fever. It is safe to say, however, that the majority of cases run their course without providing the evidence mentioned under all of these four heads, and even when present that evidence may be scanty or intermittent. Thus arterial embolism may manifest itself only by the presence of a few petechiae in the region of the clavicle or a few red blood cells in the urine at irregular intervals; or in those not infrequent cases in which the right side of the heart alone is involved the case may proceed to a fatal issue with no evidence of embolism at all. Signs of endocarditis may be scanty or completely absent when, as in one of my cases, the vegetations are implanted on the mural endocardium. All observers now agree that many cases in which repeated attempts to culture organisms from the blood are unsuccessful proceed to a fatal termination (Cotton, 1920; Lewis and Grant, 1923; Grant, 1924; Libman, 1913, 1920). This is especially true of the type known as endocarditis lenta, in which the organism responsible is a non-haemolytic streptococcus.

And, finally, in many cases fever is a late symptom (Starling, 1920), and apyrexial periods of several weeks' duration may complicate the clinical picture even at a late stage of the illness (Libman, 1913, 1920).

It is clear, then, that the diagnosis often presents difficulties, and, in fact, in some cases in which recovery has been claimed the diagnosis has not been established beyond doubt. The greatest difficulty arises in those cases in which the blood culture is persistently negative and in consequence the identity of the invading organism must be largely a matter of surmise. This I consider an important point, as it seems to me that these are just the cases which give most promise of success in treatment. Further reference is made to it below.

Spontaneous Recovery

Although such a termination is extremely rare there would appear to be no doubt that recovery has occasionally taken place. Most cases recorded are cases of endocarditis lenta, and this is not to be wondered at when it is remembered that non-haemolytic streptococci are found as normal inhabitants of the alimentary and upper respiratory tracts. Indeed, one of the problems of this disease is to know why this relatively harmless organism should assume a virulent form at all. In a search of the literature we have found records of five cases reported to have recovered from bacterial endocarditis before the advent of the sulphonamide group of drugs. Some details of these are appended in a table (see next page) together with four cases given sulphonamide therapy. One case in which surgical intervention was successful is also recorded.

A glance at the table shows one striking feature in both groups—namely, the rarity of a positive blood culture. This is true not only of the cases in which there might be some doubt as to the diagnosis but also in cases such as that now recorded, in which the evidence is practically such as to establish the diagnosis with certainty. In only two cases was a positive blood culture obtained. That of Davidson (1934)—a case of *B. coli* endocarditis—must be regarded as a rarity; while the case in the second group—that of Major and Leger (1938)—ended in death three weeks after the temperature had settled to normal, and the wisdom of its inclusion in the list is doubtful.

Anatomical Peculiarities of the Lesion

One of the problems in the pathology of bacterial endocarditis is the means by which the organisms obtain a foothold on the endocardium. On the one hand it has been held that they gain access to the tissues by being arrested in the coronary capillaries (Wadsworth, 1919), and on the other that they implant themselves directly on the surface of the valve (Keefer, 1937; Swift and Kinsella, 1917; Miller and Branch, 1923; Leary, 1932). This latter view presupposes the formation of small platelet thrombi on a previously damaged valve, such thrombi offering passing organisms a foothold and nidus for their establishment (Grant, Wood, and Jones, 1927-9). In either case the resulting vegetation is found to contain organisms aggregated in quite large masses near the periphery of the vegetations (Wright, 1925). The therapeutic problem would appear to be not simply that of controlling the septicaemia but that of reaching the depth of these foci.

The absence of bacteria from the blood in many cases of bacterial endocarditis has led to the further observation that the antibody titre is often at a high level, even in the septicaemic cases (Wright, 1925; Kinsella and Garcia, 1925-6). Wright mentions a case with septicaemia of fifty

Table giving Details of Ten Cases of Recovery from Bacterial Endocarditis

Author	Period of Observation	Embolism	Endocarditis	Blood Culture	Fever	Treatment	Recorded Effect of Treatment
Libman 1 ..	10 months	Spleen plus. Conjunctival haemorrhages. Petechiae	Mitral	5 negative	Not recorded	Not recorded	Nil
Libman 2 ..	2 years	Spleen plus. Microscopical blood in urine	Mitral and aortic	1 negative	" "	" "	"
Libman 3 ..	17 months	Skin petechiae. Microscopical haematuria	Mitral	2 negative	101° to 103°	" "	"
Davidson ..	8 years	None	Changing murmurs. Valve lesion not specified	3 positive; <i>B. coli</i>	103° to 105°	Hydrarg. perchlor. gr. 1/32 given three times. Polyvalent anti-streptococcus serum	Improvement in general condition dated from serum administration
Gibson (1920)	Not mentioned	Petechiae in crops. Haematuria	Aortic	Negative	99.4°	Perchloride of mercury intramuscularly, gr. 1/16	Improved. Discharged convalescent
Manson-Bahr 1	2 years	None	Mitral	4 negative	101°	Prontosil 6 tablets daily plus 5 c.cm. subcutaneously. Later 5 c.cm. intramuscularly daily for 24 days. Total dosage 120 c.cm.	Definite improvement immediately. Temperature fell to normal within 10 days of starting treatment. Up in one month. Clubbed fingers disappeared
Manson-Bahr 2	16 months	Spleen plus	Aortic?	2 negative. Haemolytic streptococci in urine. W.R. plus 1 positive; 7 further negative	102.6°	Prontosil soluble 95 c.cm. in 4 days; stopped 4 days; then 5 c.cm. for 10 days	Definite. Temperature normal 6 days after first intramuscular injection
Major and Leger	6 weeks	Petechiae. Osler's nodes	Mitral and aortic	1 positive; 7 further negative	100.8°	Prontosil 10 c.cm. b.d. and 10 grammes by mouth, 2 transfusions, each 500 c.cm.	Temperature normal 1 week after starting treatment. 7 further blood cultures negative. Died 29 days after temperature had fallen to normal, and 12 days after treatment with prontosil stopped. P.M. showed healing vegetation on mitral valve. On aortic valve some Gram-positive diplococci deep beneath healed surface
Andrews ..	5 months	Petechiae in crops. Osler's nodes. Haematuria. Cerebral squint. Spleen plus	" "	Negative	100° to 103°	Sulphapyridine	Immediate. Temperature fell to normal with each course of treatment. Remained normal after third. Petechiae and haematuria disappeared
Hamman and Rienhoff	2 months	Spleen plus. Blood in stools	None. Vegetations in aneurysmal sac	3 positive; <i>Strep. viridans</i>	102° to 103°	Excision of arteriovenous aneurysm between external iliac artery and vein	Immediate fall in temperature and general improvement. Discharged from hospital one month after operation

organisms per c.cm. of blood in which it was found that each cubic centimetre of the patient's blood was in fact capable of dealing with some thousands of organisms from a laboratory culture in addition to those constituting the septicaemia. The persistence of the septicaemia would therefore appear to be explicable only by multiplication of the organisms in the focus of infection and overflow into the blood stream. Confirmation of the correctness of this view is provided by the case of Hamman and Rienhoff (1935), in which an endocarditis localized in an aneurysmal sac was cured by excision of the aneurysm. It would seem that in those cases which are persistently bacteria-free the organisms are killed off as fast as they appear in the blood stream. This is probably associated with the presence of fewer organisms in the vegetations or with an infection by a less virulent strain (Wright, 1925; Keefer, 1937).

In view of the fact that nearly all the cases recorded as having recovered—whether spontaneously or as a result of treatment—have been bacteria-free, it seems reasonable to expect that under suitable treatment with a member of the sulphonamide group of drugs many of these patients could be saved. I have treated two cases of bacterial endocarditis with sulphapyridine (M & B 693). In one, that of a woman aged 55, a pneumococcus had been isolated by blood culture. The immediate effect of the sulphapyridine was dramatic. The temperature fell to normal and remained normal so long as adequate concentrations of the drug were maintained. This patient was in an advanced state when she came under observation. She died two weeks after starting treatment, and at

necropsy a mural vegetation the size of a walnut was found in the right ventricle. It was clear that intravascular sterilization of such a mass was unattainable, and that all we had done was to diminish the degree of septicaemia, with corresponding amelioration of the symptoms.

The second case, which is recorded below in greater detail, came under treatment at an early stage of the illness. The patient presented the clinical picture of endocarditis lenta, and, in spite of the absence of bacteriological confirmation, treatment with sulphapyridine was instituted and the patient recovered.

Case History

The patient, a retired barrister aged 68, was first seen in October, 1938. He was then complaining of frequency of micturition, which on investigation proved to be due to a *B. coli* infection. This cleared up under treatment in a fortnight. On this occasion in the course of a general examination the presence of aortic regurgitation was noted. The radial pulse was collapsing; the apex beat was felt in the fifth space, one inch outside the mid-clavicular line. A soft diastolic murmur was heard down the left border of the sternum. No mitral murmur was heard. The blood pressure was 200/70. As the lesion was symptomless and the life well regulated no special precautions were taken beyond informing the patient's wife and arranging that certain long journeys should be discontinued. He remained in good health after this for eight months. He came under observation again on June 10, 1939. He was then in bed, and complained of gastric discomfort and pain in the legs, especially in the region of the joints. This began ten days previously, and he attributed it to the eating of mushrooms at his club. He said he had been

feverish for a few days after this, that the temperature had settled, and that he had then had a heavy dinner, which caused his temperature to shoot up again to 103°.

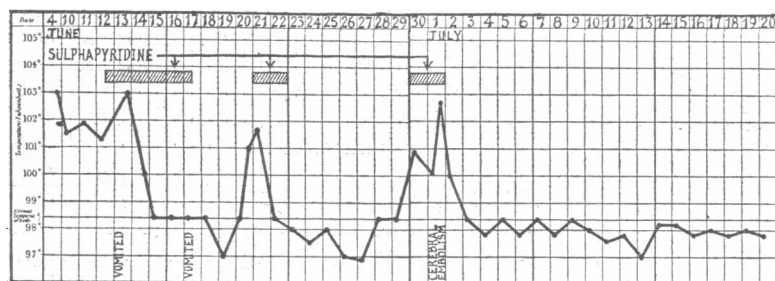
EXAMINATION

The patient was of spare build, with sallow complexion. His temperature was 101.2°. Numerous petechiae were present and new spots were found each day for the next two weeks. The extent of the rash may be judged from the observation that one could always count eight or ten spots on the abdomen and that it was most profuse on the legs. Under a lens many of the spots could be seen to have white centres. Frequent ectopic beats were noted. The aortic diastolic murmur had changed in character and could be heard all over the lower half of the sternum. There was a well-marked apical systolic murmur and the second pulmonic sound was exaggerated. The blood-pressure reading was 190/60. Some abdominal distension was noted, and the tip of the spleen was just palpable some days later. Signs of the embolic process were not lacking. On the third day after the first observation he developed a dark discoloured patch on the inner side of the right ankle. The nature of this was not realized till typical Osler's nodes appeared on the fingers. In the first week fan-shaped conjunctival haemorrhages and haematuria were also noted. Urinalysis on June 12 showed a specific gravity of 1014, albumin plus, moderate reduction with Fehling's and Benedict's solutions, and no evidence of ketosis. The deposit contained red blood cells and occasional leucocytes. A fasting blood-sugar estimation carried out in view of the glycosuria gave 262 mg. per 100 c.cm. The glycosuria was also probably embolic in origin, as it cleared in a few days, and the blood sugar is now normal. On June 30, eighteen days after starting treatment, the patient suddenly developed signs of cerebral embolism, in the form of a paralytic divergent squint. The diplopia resulting from this is now his sole disability.

A blood count taken on June 12 revealed haemoglobin, 95 per cent.; red blood cells, 5,100,000 per c.mm.; colour index, 0.9; mean diameter, 7.2 μ; white blood cells, 9,600 per c.mm.—polymorphs 71 per cent., lymphocytes 20 per cent., monocytes 9 per cent. Platelets numbered 190,000 per c.mm. A blood culture taken on the same day was negative after seven days' incubation.

TREATMENT

Sulphapyridine was begun on June 12. In all, three courses were given, using the oral method of administration for the first two and the intramuscular route for the third. Nausea



was a troublesome symptom, and was equally marked when the drug was given intramuscularly. For this reason the doses aimed at were not attained. The first course only was fairly successful: in five days the patient had 12 grammes. On the second occasion we had to be content with half this amount, administered in two days; and on the third we gave 2 grammes intramuscularly.

The temperature fell almost immediately on starting the first course (see Chart); after twenty-four hours' administration it was normal. It remained normal so long as the drug was continued and for three days after stopping it; then it rose again. Simultaneously with this rise we resumed treatment, with a similar result. After the third series, although we had

not up to then noted any improvement in the patient's general state, the temperature fell to normal and remained down. Constipation was a troublesome symptom throughout and necessitated frequent changes of aperient. A specimen of urine on June 26 still contained microscopical blood and some hyaline and granular casts. Convalescence was uneventful. He got up three weeks after the temperature finally settled.

Seen on October 10, he was then acting as chairman of a military services hardships committee and also of an unemployment assistance tribunal. He walked to and from that consultation—a distance of four miles. He said he felt very well, though he thought he had been slow in picking up strength. The squint was less obvious. There was no increase of cardiac enlargement, though signs of well-marked mitral and aortic valve disease were present. The blood pressure was 190/70. The electrocardiogram revealed left axis deviation but no evidence of muscle failure. There were no petechiae and the spleen could not be felt. The urine revealed no albumin, blood, or casts on microscopical examination.

Comment

The amounts of sulphapyridine given in this case were inadequate when judged by the standard of dosage in common use, and yet there would appear to be no doubt that administration of the drug was the important factor in saving the patient's life. Further, one is inclined to wonder whether the profusion of the embolic process, indicating as it must have done a considerable disruption of the bacterial focus on the endocardium, presented the optimum condition for access by the drug to the organisms. It may well be, indeed, that the final victory in the treatment of this disease will be won by the combined use of a sulphonamide derivative with some agent directed towards lysis of the early thrombotic foci on the heart valves (Best, 1938).

In view of the published cases it seems clear that every case of bacterial endocarditis in which the identity of the invading organism can be determined should be treated by the suitable member of the sulphonamide group. Apart from the possibility of cure discussed above, life is prolonged and great relief obtained from the drenching sweats, the limb pains, and other troublesome symptoms (Whitby, 1938a, 1938b).

In cases of subacute bacterial endocarditis failure to obtain a positive blood culture should not lead to delay in instituting treatment. It is the experience of nearly all observers that those cases which are found to be negative continue to be negative (Wright, 1925; Cotton, 1920; Lewis and Grant, 1923; Grant, 1924; Libman, 1913, 1920). Further, if the views expressed above are correct it is in these bacteria-free cases that success is most likely. Time should therefore not be wasted on repeated attempts to obtain a positive blood culture. In cases presenting the triad of symptoms multiple embolism, endocarditis, and fever, sulphapyridine should be given immediately in adequate amounts (Maegraith and Vollum, 1938; Buttle, 1939; Segal, 1936).

Summary

A case is recorded of recovery from bacterial endocarditis. Treatment was by sulphapyridine. The diagnostic and therapeutic difficulties are briefly discussed.

My best thanks are due to Lord Horder, who kindly saw this case with me; to Dr. F. D. M. Hocking, who carried out

the pathological investigations; and to the lady whose nursing skill and unwavering optimism contributed in no small measure to the patient's recovery.

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NOCTURNAL ENURESIS

BY

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The prevalence of nocturnal enuresis among children, especially of the poorer class, has been something of a revelation to those concerned with evacuation. Most mothers are very reticent about bed-wetting in their own children, and until the children were obliged to leave home the secret was so well kept that the high incidence of bed-wetters was not even guessed.

The causes of bed-wetting are various, and therefore it is essential to investigate each case individually and to deal with it in relation to the cause rather than to the effect. The general attitude to this unfortunate habit is one of horror and disgust on the part of strangers and shamefaced acceptance on the part of the mother. Hostesses of evacuated children are sorely tempted to treat the offending child with reproach and punishment coupled with sarcastic references to his mother and his upbringing.

Training in Cleanliness

One of the commonest causes of bed-wetting is the lack of training in cleanliness in infancy and early childhood. This is the fault of the mother, and may be due to sheer laziness or indifference or to an unconscious desire to keep the child dependent and a "baby." This latter motive is frequently unearthed when children are brought to child-guidance clinics and the cases fully investigated by experts. When a new baby arrives the mother's attitude changes and she now wants the older child to become independent as soon as possible so that she may be free to look after the infant. She is therefore apt to begin to scold and punish the bed-wetter, quite failing to realize that she alone is to blame. If this treat-

ment fails—and it usually does—the child may become the black sheep of the home, nagged and sneered at until his self-confidence is destroyed or until he feels that every man's hand is against him and that rebellion against life is his only means of escape. He is indeed fortunate if he comes to a clinic early, where his difficulties are understood and can be dealt with wisely. This lack of training is certainly the commonest cause and accounts for a large proportion of cases.

It is noteworthy that bed-wetting is much more prevalent among boys than among girls, and the reason for this has never been satisfactorily discovered. It is probable, however, that in many cases it is due to the greater indulgence which mothers show to their sons and their wish to keep them closely attached to themselves. In such a case the obvious treatment is to get the mother's confidence and co-operation and to enlist her help in patient training of the child to independence and self-reliance in every way. By holding up to the child the ideal of growing up as a privilege and a pleasure, and by giving him opportunities for exercising responsibility and for self-expression, he soon realizes that bed-wetting belongs to the "babyish" things which are unbecoming to his dignity and self-respect.

It may be laid down as an axiom that, whatever the cause of bed-wetting, scolding and punishment should never be employed: first, because it never cures the trouble; and, secondly, because it seriously damages the child's personality and often results in a further regression to babyishness and a timidity and fear of facing life, or in a sense of grievance and injustice that it is being blamed for a thing of which it is not even aware and that it knows to be entirely out of its control. These attitudes of mind, if allowed to continue, lead to an asocial or anti-social outlook which may persist and hamper both the individual and the community in which he lives.

Physical Causes

Among the commonest of the physical causes of bed-wetting are the following: (a) Extreme acidity or alkalinity of the urine, and concentration of the urine so that it becomes irritant. In this connexion the attempt to cure bed-wetting by restricting fluids should be mentioned. Usually it makes matters worse, because it tends to produce increased concentration of the urine and therefore to render it more irritant. This is certainly not a method to be used without medical advice and frequent testing of the urine. (b) Threadworms are also a fairly common cause. (c) In boys irritation of the prepuce by an accumulation of the greasy material normally found there is not unusual. The treatment is gently to draw back the prepuce with a moist cotton-wool swab and remove the smegma with olive oil. Zinc or some other bland ointment should be applied nightly. (d) In girls there is not infrequently a vaginitis that leads to redness and inflammation of the parts around the opening of the urinary passage. Zinc sulphocarbolate or a mild mercury ointment is helpful in relieving this condition. (e) Where there is frequent passing of water by day as well as by night a cystitis is to be suspected.

Psychological Causes

The causes which are primarily due to the child itself are all psychological, but they are nearly all unconscious and not in any sense the child's fault. These include:

Mental Defect.—A child whose mental development is retarded or permanently damaged by failure of the brain