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For the past year a new residential school for spastics, "Scotsraig," has been open in Paisley. It is under the direction of the Scottish Council for the Care of Spastics. Once extensions have been completed, the school should have enough places to educate and treat suitable children from the West of Scotland. Cases are screened before acceptance by a panel consisting of an orthopaedic surgeon, a paediatrician, a child psychiatrist, and an educational psychologist. Apply for further details to the social worker, "Scotsraig," Park Road, Paisley.

BACTERIAL ENDOCARDITIS

SURVEY OF PATIENTS TREATED BETWEEN 1945 AND 1956

BY

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Sulphonamides reduced the mortality of bacterial endocarditis from some 99% to 95% (Friedberg, 1950), but with the introduction of penicillin the cure of most patients at last became a possibility. The manner in which penicillin should be employed was elucidated in this country largely as a result of the Medical Research Council trials which were set up in 1945 (Christie, 1946, 1948, 1949; Cates and Christie, 1951). However, the Registrar-General (1955) showed that in 1949 the early mortality of bacterial endocarditis in the majority of teaching hospitals was 25% (of 124 cases), and for a smaller number of regional board hospitals the mortality was 31% (of 26 cases), while in 1951 these figures were still 19% (of 126 cases) and 40% (of 35 cases) respectively. The yearly mortality due to bacterial endocarditis in England and Wales (Registrar-General, 1955) showed a slight decline from 1938 which became steeper after 1944 when penicillin became available, but this improvement affected females to a greater extent than males. Since 1952 the mortality among males has remained more or less constant, while for females there has been a further slight decrease (Fig. 1).

Because of the persistence of bacterial endocarditis as a cause of mortality, it was decided to survey all the patients who had been treated in this hospital for the disease during the period that antibiotics had been freely available. This survey therefore covers the years 1945 to the end of 1956, and concerns a total of 82 patients (58 male and 24 female); their heart

Fig. 1.—Yearly total deaths in England and Wales due to bacterial endocarditis.

TABLE I.—Heart Lesions—All Patients

Rheumatic heart disease ..	..	..	63
Significant aortic disease ..	..	..	37
Simple mitral stenosis ..	..	..	7
Congenital heart disease ..	..	..	13
Ventricular septal defect ..	..	..	7
V.S.D. and pulmonary stenosis ..	..	..	1
Persistent ductus arteriosus ..	..	..	1
Aortic stenosis ..	..	..	3
Multiple defects ..	..	..	1
Spirochaetal aortic disease ..	..	..	2
Arteriosclerotic heart disease ..	..	..	4

lesions are shown in Table I. In a few cases initial investigation or treatment had been started elsewhere. All patients were traced and survivors followed until 1956 or 1957 with the single exception of one female who went abroad in 1954, four months after cure. Among these 82 patients there were, because of second attacks, a total of 97 separate infections, 22 of which

FIG. 2.—Present series. Age groups and bacteriology.

(15 male and 7 female) were bacteriologically negative. The age distribution of the patients with these infections is shown in Fig. 2.

Results of Treatment

Of the 14 patients who had survived treatment in 1945 one died after reinfection with a different and resistant organism, a further two (both having severe rheumatic heart disease) died as a result of heart failure three years after cure, while 11 patients were alive 11 years later.

Since 1946 51 bacteriologically positive patients have been treated, but 15 (29%) failed to survive treatment (Table II), while a further 13 have died (Table III), seven of them within two years of treatment and from causes attributable to the results of their infection, making a total early and late mortality, therefore, of 43%. For the remaining patients of this group the present duration of survival is shown by Table IV.

TABLE II.—Bacteriologically Positive Patients Dying Before Discharge

Year	Sex	Age	Total Length of Illness (Months)	Organism	Remarks
<i>Undiagnosed in Life</i>					
1948	F	54	?	—	} S.B.E. incidental to other disease Cerebral embolus
1956	M	73	?	—	
1956	M	72	4	—	
<i>Resistant infections uncontrolled at death</i>					
1955	F	52	1	Coag. pos. staph.	—
1953	M	40	3	<i>Staph. albus</i>	—
1953	M	52	2	<i>Corynebact. diphtheroid</i>	—
1947	M	63	20	<i>Str. viridans</i> (resist.)	—
1951	M	63	6	<i>Str. faecalis</i>	—
1955	F	19	20	" "	—
<i>Uncontrolled at death</i>					
1955	M	36	2	Micro-aerophil. strep.	Coronary embolus—2nd week of treatment
1950	M	8	5	" "	Poor response to treatment
1956	M	58	5	<i>Str. viridans</i>	After 1 month's treatment—cerebral embolus
<i>Controlled at death</i>					
1954	M	22	7	<i>Srep. viridans</i>	Heart failure 1 month after completing treatment
1954	M	23	7	" "	Heart failure 6 weeks after completing treatment
1950	F	36	?	<i>Str. faecalis</i>	Heart failure 2 weeks after completing treatment

TABLE III.—Bacteriologically Positive. Deaths After Cure

Sex	Age at Death	Infection		Length of History before Curative Treatment (Mths)	Remarks	Death	
		Organism	Year			Time from Cure (Mths)	Cause
M	61	Str. viridans	1955	6	Heart failure before treatment	1	Heart failure. Uraemia
M	51	" "	1954	5	Valve rupture 1 month from cure	3	Heart failure
F	55	" "	1948	1	Heart failure during treatment. Syphilitic heart disease	3	" "
M	49	Bact. fusiformis	1953	3	Heart failure during treatment	4	" "
M	62	Str. viridans	1954	2	" "	4	" "
M	24	Str. viridans (resist.)	1951	11	" "	6	" "
M	26	Str. viridans	1946	3	—	24	Rupture old cerebral mycotic aneurysm
F	69	Non-haemolytic strep.	1953	1	Heart failure 4 months after cure. Syphilitic heart disease	31	Heart failure
M	37	Str. viridans (resist.)	1946	5	Fibrillation 4 years after cure	60	" "
M	32	Str. viridans	1948	1	Sudden death	49	? Cerebral embolus
M	49	" "	1950	1	Second attack	72	2nd cerebral embolus

Two other deaths were unrelated to heart lesion.

TABLE IV.—Bacteriologically Positive Patients Surviving

	Year from Cure of First Attack										
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th
No. of patients	2	5	1	0	1	2	3	3	2	1	3

Delay in Diagnosis

The delay in diagnosis from the time of onset of symptoms has been assessed where possible and is shown in Fig. 3; this indicates also the number of patients who either knew that they had congenital heart disease, had had previous bacterial endocarditis, or who would have suggested the possibility of an abnormal heart by giving a history of rheumatic fever. That delay could be considerable is emphasized by the number of patients who had been infected for over three months before being correctly diagnosed. Since a high index of suspicion for bacterial endocarditis must be entertained in any patient having an abnormal heart, the large proportion of patients in this series who would on history-taking have indicated such an abnormality is of interest.

It was obvious that, when less typical features of endocarditis predominated, delay in diagnosis tended to be considerable, for such features may blind the clinician to the other signs and symptoms which a fuller history and examination would reveal.

The presence of pains in joints often appeared to confuse, and in eight patients joint pains, sometimes in a single joint, were a predominant complaint. In a further two patients effusions into a knee-joint were found on initial examination. Sometimes there may be confusion with rheumatic fever, and indeed two patients were so misdiagnosed initially,

FIG. 3.—Present series. Delay in diagnosis.

while in a third, on good grounds, both diseases were assumed to be present.

Bacterial endocarditis may start with or follow immediately upon an infection of the upper respiratory tract, and in this series diagnosis was delayed in five patients who were diagnosed originally as having influenza, failure to recover from this being attributed to post-influenzal depression.

Old age (4 patients), the presence of other conditions (3), gross purpura (2), and short courses of antibiotics for unexplained fever (8) were further causes of delay.

In most cases murmurs were obvious, and little doubt could be entertained concerning the abnormality of the heart, but in each of three patients the only abnormality present was a short apical systolic murmur whose significance could easily have been overlooked.

Certain other aspects, while not greatly delaying diagnosis, gave cause for comment. Retinal haemorrhages were a common feature, but in four patients papilloedema, whose occurrence in cases of bacterial endocarditis was well reviewed by Falconer (1910), was also present. In one of these patients the association of papilloedema and mental change caused serious consideration as to whether an intracranial tumour might also be present, but the mental changes improved with treatment of the endocarditis and no intracranial abnormality was subsequently shown at post-mortem examination. Apart from cases with cerebral embolus, mental confusion was a marked feature with two patients, both of whom were in the later age groups, in which mental impairment often accompanies infection.

Investigations such as the erythrocyte sedimentation rate can usually be relied upon to give some indication of infective processes, and in only two patients of the present series was the initial recording (Westergren) less than 10 mm. in one hour, while no values were below 5 mm. The haemoglobin level sometimes drew attention to the disease, but its degree of departure from normal tended to be related to the length of history, so that it becomes of less value if the accent is to be on early diagnosis. The total white blood count was of no diagnostic value: of 51 cases, it was less than 5,000 in 3, between 5,000 and 10,000 in 25, between 10,000 and 15,000 in 16, and between 15,000 and 20,000 in 7.

Only four patients who were bacteriologically positive had established auricular fibrillation when the disease set in, and two of these were examples of post-operative staphylococcal endocarditis; a further three patients had fibrillation during treatment. By contrast auricular fibrillation was established in 5 out of 22 bacteriologically negative patients at the onset of their disease.

Precipitating Factors

Eleven patients gave a history which strongly suggested that extraction of infected teeth without antibiotic cover was the precipitating factor; nine of them were infected with a *Streptococcus viridans*, while two had a micro-aerophilic streptococcus. Questioning for a history of rheumatic fever or of known heart disease would have obtained a positive answer in seven of these patients.

Records concerning dental extractions performed under antibiotic cover are not complete, but at least 43 patients who have previously had bacterial endocarditis had teeth extracted, on 57 occasions, under antibiotic cover without subsequent incident. Two patients, however—one with and one without a previous history of bacterial endocarditis—were infected following dental extractions under penicillin cover. One of these became infected with a highly resistant organism and has been reported already (Cates, Christie, and Garrod, 1951). The second patient, who had congenital aortic stenosis, was investigated by cardiac catheterization and cardioangiography on August 29, 1951; procaine penicillin, 300,000 units, was given twice daily on the 29th and 30th and the wound healed well. On September 5 eight

teeth were extracted, crystalline penicillin, 500,000 units, being given one hour before extraction, followed by procaine penicillin, 300,000 units twice daily, starting at about the time of extraction and carried on for three days. Symptoms started soon afterwards, and subsequently blood culture yielded a *Str. viridans* having approximately four times the resistance to penicillin of the Oxford staphylococcus.

Ten patients were found to be edentulous, although in none of these was the absence of buried roots confirmed by radiology. Table V shows the relevant details of these cases. The patient infected with a micro-aerophilic strepto-

TABLE V.—Patients Edentulous on Admission

Sex	Age	Organism
M	56	<i>Str. faecalis</i>
M	49	<i>Bact. fusiformis</i>
M	72	Undiagnosed in life
M	73	"
M	45	Negative
M	46	"
F	50	"
F	52	"
M	67	Micro-aerophilic streptococcus
M	62	<i>Str. viridans</i>

coccus had had a dental clearance four months earlier, and this appeared to be the precipitating factor. Only one edentulous patient was infected with *Str. viridans*, and this was proved to be highly resistant. He was found on admission to have an infected ulcer in the mouth due to the abrasive effect of ill-fitting dentures, and it was thought possible that his infection had resulted from this.

One case was of interest in that it demonstrated the manner in which a focus of infection may persist at the site of dental abnormality. A 24-year-old man had had two teeth extracted in November, 1946, but there was then a gap of seven months before the onset of bacterial endocarditis. He was admitted to hospital on March 26, 1948, having been treated at home with penicillin (the type of preparation being unknown), 500,000 units twice daily, from March 19 to 26. Blood culture taken on April 16 was the first to yield a positive result, growing a micro-aerophilic, slightly α -haemolytic, streptococcus having half the resistance to penicillin of the Oxford staphylococcus as judged by bacteriostatic tests. Treatment, begun on April 26, consisted of crystalline penicillin, 62,500 units by intramuscular injection every three hours, the penicillin titre of the serum just before the next injection was due being 0.09 u./ml. After an initial response further spikes of fever were recorded, but another blood culture on June 1 was sterile. Full dental examination on admission had shown healthy gums and teeth apart from one tooth which on x-ray examination showed apical rarefaction. Extraction of this tooth on June 11 revealed a granuloma attached to one of the roots. Culture from the surface of this yielded a very scanty growth of indifferent organisms, but an aerobic culture from the interior of the granuloma yielded a profuse growth of a streptococcus which was considered to be the same organism as had been obtained from the blood. Subsequent recovery was uninterrupted.

Of those cases infected with a *Str. viridans* (totalling 47) and with no history of recent dental manipulations, two

TABLE VI.—Precipitating Factors—Non-dental

Year	Age	Sex	Organism	Source of Infection
1950	62	M	<i>Str. faecalis</i>	Prostatectomy
1950	36	F	" "	Therapeutic abortion
1954	19	F	" "	"
1952	25	F	" "	Abortion
1955	70	F	" "	Operation for urethral caruncle
1956	34	M	Micro-aerophilic strep.	Aural sepsis
1948	48	M	Coag.-neg. staph.	Septic spot scratched by comb
1955	52	F	Coag.-pos. staph.	Infected eczema
1956	21	F	" "	Boil
1953	40	M	Coag.-neg. staph.	Mitral valvotomy
1955	40	F	Coag.-pos. staph.	"
1954	31	M	Negative	Cardiac catheter

patients on full dental examination, which included x-ray films of the teeth, had no evidence of disease of teeth or gums.

Apart from 11 cases attributable to dental sepsis the precipitating factor could be identified in 12 patients; the details are shown in Table VI.

TABLE VII.—Results of Blood Culture

Organism	No. of Infections	No. of Cultures to Obtain Positive			Organism	No. of Infections
		1	2	More than 2		
<i>Str. viridans</i> : Insufficient information	8				<i>Staphylococcus</i> (coag.-neg.)	3
Sensitive to 0.04 u. or less penicillin/ml.	27*	25	1	1	<i>Staphylococcus</i> (coag.-pos.)	3
Sensitive to 0.04-0.2 u. penicillin/ml.	6	6			<i>Corynebacterium diphtheroid</i>	1
Sensitive to >0.2 u. penicillin/ml.	6	6			<i>Bact. fusiformis</i>	1
Micro-aerophilic streptococcus	8†	6	1	1	Undiagnosed before death	3
Other haemolytic streptococci	2				Bacteriologically negative	22
Non-haemolytic streptococcus	1	1				
<i>Str. faecalis</i>	6					

* Six with fewer than 10 colonies per ml.

† Two very resistant; 6 sensitive to <0.09 u. penicillin per ml.

Organisms

Table VII shows the details of recovery of organisms, the proportions of the types commonly found being very similar to those reported in the literature. In two cases in which blood culture yielded scanty growth of organisms and there was doubt about whether they were in fact contaminants, agglutination tests with the patients' serum enabled the question to be settled. Although growth sometimes did not appear before the seventh day, most organisms, particularly the *Str. viridans*, were recovered with the first blood culture.

Morbidity

Some of the complications found are discussed below and shown in Tables VIII to X; the more serious of these considerably influenced the mortality of the disease.

Mycotic aneurysms occurred in eight patients, being commoner in young males (Table VIII). The 67-year-old

TABLE VIII.—Arterial Mycotic Aneurysms

Age	Sex	Organism	Site	Remarks
21	M	<i>Str. viridans</i>	Brachial	Excised during treatment
40	F	Staph. (coag.-pos.)	Popliteal	" " "
24	M	Micro-aeroph. strep.	Int. iliac	" " "
26	M	<i>Str. viridans</i>	Inf. gluteal	Excised 3 months after treatment
67	M	Micro-aeroph. strep.	Radial	Tied soon after treatment
23	M	<i>Str. viridans</i>	Popliteal	Int. carotid tied 1 month after treatment.
26	M	" "	Hepatic	Found at necropsy
52	M	<i>Corynebacterium</i>	Cerebral	Burst 2 years after bacteriological cure
			Popliteal	Present at death—infection uncontrolled

man had elsewhere been treated with corticotrophin when a biopsy of a lump had mistakenly been thought to indicate a diagnosis of polyarteritis nodosa. Lambert Rogers (1956) also noted a preponderance of young males when he reviewed the association of mycotic aneurysm and bacterial endocarditis.

Major embolic phenomena occurred on 39 occasions, as shown in Table IX, renal and splenic emboli being excluded because of the uncertainty of records. Laparotomy was performed on one patient who presented with superior mesenteric embolus and he survived, but the other cases of this condition were diagnosed clinically and treated conservatively, and all but one survived.

Six patients had considerable renal involvement early in the disease, with proteinuria and many casts; three of them

TABLE IX.—Major Embolic Phenomena

Artery	No. of Patients	Remarks
Cerebral	5	Severe, with little or no recovery (early death in 2)
Coronary	6	Mild, with considerable recovery
Mesenteric	3	All early death
Pulmonary	5	Laparotomy in one
	10	4 patients with V.S.D. had 7 major infarcts. Pleural effusion in 3 patients
Retinal	1	
Upper limb: proximal	1	
Lower limb: distal	5	
Spleen and kidney	3	
		Not presented

TABLE X.—Valve Rupture

Sex	Age	Organism	Length of History before Treatment (Months)	Site	Time of Rupture in Relation to Treatment (Weeks)	Length of Survival after Rupture (Weeks)
Proved at Necropsy						
M	22	<i>Str. viridans</i>	14	Aortic	During	4
M	51	" "	5	Mitral	3 after	6
M	23	" "	4	Aortic	20 after	1
M	24	" "	10	" "	During	16
M	52	<i>Corynebacterium diphtheroid</i>	Few	Sinus of Valsalva to right auricle	"	Nil
Diagnosed clinically—unproved at necropsy						
M	49	<i>Bact. fusiformis</i>	3	? Mitral	During	24

survived, one continuing with a slight degree of proteinuria; in those who did not survive, renal failure contributed significantly to death. Progressive renal disease is a complication which can follow cure of endocarditis, but in this series no cases of late renal failure have so far been encountered.

Damage at the site of injection, which was commoner with the early forms of penicillin injections, has been unusual of recent years, but a sterile abscess was seen in two patients, each of whom, infected with a resistant organism, was being treated with streptomycin and with large doses of penicillin. The possibility of tissue reaction is, however, important in so far as it may contribute to persistence of fever and a raised erythrocyte sedimentation rate.

It was often the case with patients treated in 1945 that their fever did not abate until treatment stopped, and the problem has arisen in two cases of recent date. In one of these the persistence of some fever led to the abandonment of the correct form of treatment, which was not resumed until some months later, while in the other the dosage of antibiotics was probably pushed unnecessarily high. In case of doubt the bacteriologist can help in deciding whether there is an adequate bactericidal level of antibiotics in the serum.

Urticaria occurred in five patients treated with penicillin and was associated in one with alarming collapse and a rigor soon after her first injection. In three patients these reactions were severe enough to hold up treatment, but in each case desensitization was effected rapidly by the simultaneous use of penicillin and an antihistamine, as has been described by Maslansky and Sanger (1952), Balme and Dormer (1954), and Robinson and Binns (1954).

After streptomycin treatment three patients had no vestibular function remaining, while in a fourth there was considerable impairment of function. When penicillin is used in combination with streptomycin the dose of 4 g. a day of the latter, as recorded by Cates *et al.* (1951) and still quoted (Brewis, 1956), is probably excessive, 2 g. a day being now usually employed, although in particular circumstances and with the guidance of the bacteriologist this may require modification. There is evidence that streptomycin given as a mixture of streptomycin sulphate and dihydrostreptomycin results in less damage to the eighth nerve, but the more severe disabling effects of dihydrostreptomycin on the auditory component must be borne in mind.

Recurrence

Relapse of infection in some patients at the start of this series occurred early, and it is apparent that the dosage of antibiotics had been inadequate. All were finally cured by more intensive treatment. In a patient treated more recently the infection relapsed early when it was assumed to have been eradicated; the case report is here presented.

A girl, who had a history of two attacks of rheumatic fever and whose heart showed signs of mitral stenosis and aortic incompetence, had teeth extracted without antibiotic cover in 1951 at the age of 17. Within two months the full clinical picture of bacterial endocarditis developed, but diagnosis was delayed a further four months. Two blood cultures then proved to be negative, but she responded completely to a six-weeks course of crystalline penicillin, 500,000 units every three hours. Two years later, in October, 1953, teeth were extracted under cover of penicillin, and one month later a therapeutic abortion was carried out without antibiotic cover. Again she had symptoms of bacterial endocarditis, and in December a *Str. faecalis* was recovered from the blood. From then on, until she was referred for treatment nine months later, she received six different antibiotics, alone or in combination according to 11 dosage schedules, with little more than temporary control of the disease. In September, 1954, the *Str. faecalis* was again recovered and put up against penicillin, streptomycin, oxytetracycline, chloramphenicol, erythromycin, and bacitracin, alone and in pairs, but only penicillin (10 u./ml.) and streptomycin (10 µg./ml.) combined exerted a bactericidal effect and sterilized the medium. She was treated with crystalline penicillin, 2.5 mega units three-hourly for six weeks, together with streptomycin, 1 g. twice daily for the first week, followed by 0.5 g. twice daily, and this dosage gave adequate blood concentration. She rapidly became afebrile and remained so for six weeks after completion of the drug course before being discharged from hospital, but two weeks after that the signs and symptoms of infection recurred and *Str. faecalis* was again found. Unfortunately she was not referred back for treatment. Further palliative courses of bacteriostatics were given elsewhere and she died in August, 1955, necropsy revealing unhealed vegetations on both mitral and aortic valves extending widely on to the wall of the left atrium and left ventricle.

The relapse after the major course of combined penicillin and streptomycin was surprising, although it was realized that the dosage of streptomycin was being kept to a minimum to prevent extension of the already severe vestibular damage. Probably a longer course should have been given in view of the very long history and presumably large vegetations.

TABLE XI

Sex†	Age	First Infection		Second Infection		Time Interval Yrs. Mths.	Remarks
		Year	Organism	Year	Organism		
M	21	1945	<i>Str. viridans</i>	1949	Haem. strep.	4 1	Clinically certain
F	22	1945	" "	1954	Negative	9 0	
M	45	1945	" "	1948	Coag.-neg. staph.	2 3	Possibly same organism
M	25	1945	" "	1945	<i>Str. viridans</i>	0 10	
M	16	1945	" "	1955	Haem. strep.	9 8	
M	19	1945	" "	1950	Coag.-neg. staph.	4 10	Died Second followed dental ext.; diff. sensitivity
M	38	1945	" "	1956	Micro-aero. strep.	11 9	
M	57	1945	" "	1950	<i>Str. faecalis</i>	5 0	
M	37	1946	" "	1950	<i>Str. viridans</i>	4 8	Some doubt
M	20	1947	" "	1952	Negative	4 9	
M	26	1947	" "	1949	"	2 10	
M	24	1948	Micro-aero. strep.	1956	"	8 2	Organisms had similar sensitivity
F	11	1949	<i>Str. viridans</i>	1952	<i>Str. viridans</i>	2 11	
M	19	1950	" "	1953	" "	2 6	Died
F	16	1952	Negative	1953	<i>Str. faecalis</i>	1 10	

In all, 15 of the 82 patients who form this series were diagnosed as having two attacks of endocarditis, the details being presented in Table XI. In 11 the underlying heart disease was rheumatic, while in 4 a ventricular septal defect was present.

Treatment

For penicillin-sensitive organisms there was experiment originally with the daily dosage of penicillin, but with the publication of the M.R.C. report in 1948 crystalline penicillin given by intramuscular injection at three-hourly intervals to a total of 2 mega units daily and for six weeks became the practice throughout the hospital. Even on this regime one patient with a sensitive *Str. viridans* infection failed to respond until the daily dosage was raised to 4.8 mega units.

The practice of treating sensitive infections with intramuscular crystalline penicillin continued through to 1957, but since about 1953 physicians have tended to use larger doses at greater intervals, the commonest regime being that of 1 mega unit every six hours. This, while adequate for most patients, proved to give inadequate control in one where the organism (a *Str. viridans*) had 1.4 times the resistance of the standard staphylococcus, and in a further patient infected with a non-haemolytic streptococcus sensitive to 0.2 unit of penicillin per ml., 3 mega units every six hours proved sufficient after 2 mega units every six hours had been inadequate.

For the resistant organisms in this series penicillin and streptomycin proved to be the most useful combination of drugs. For all the strains of *Str. faecalis* such a combination proved bactericidal, while in one strain a lesser effect was obtained with streptomycin and erythromycin and with streptomycin and oxytetracycline. Such action was not found with any other individual drug or pair of drugs from among those tested, which included penicillin, streptomycin, oxytetracycline, chloramphenicol, erythromycin, and bacitracin.

The combination of streptomycin with penicillin also effected cure in two recent staphylococcal infections. In one of these penicillin alone, while effecting stasis, did not sterilize the medium. Before referral this patient had received four antibiotics in six different combinations and schedules of dosage over a period of seven days. The other staphylococcus proved to be a slow penicillinase producer but was eliminated by crystalline penicillin, 7 mega units, together with streptomycin, 0.75 g., every eight hours over five weeks.

Bacteriologically Negative Group

This group, consisting of a total of 22 patients, five of whom at some stage had a bacteriologically positive infection, is not easy to classify but may be subdivided as follows.

Group 1.—This group consists of 16 patients who had the clinical features of bacterial endocarditis and for whom, despite negative blood cultures, there seemed no reason to doubt the diagnosis. Ventricular septal defect was present in three. Twelve patients showed response to penicillin in ordinary doses, although four died of early complications (three of heart failure and one following a cerebrovascular accident). In four patients penicillin was not sufficient or was not used alone to control the disease. One patient relapsed immediately on cessation of massive penicillin dosage and died of heart failure during chloramphenicol treatment, post-mortem examination revealing healing endocarditis of the aortic valve. One patient with congenital aortic stenosis failed to respond to penicillin in a daily dose of 2 mega units but apparently responded to a six-weeks course of penicillin, 10 mega units, combined with streptomycin, 2 g. a day, only to relapse. This combined course was repeated and controlled the disease. The other two patients were cured by a single course of penicillin and streptomycin in combination.

Group 2.—This group consists of those patients presenting with heart disease and with fever, atypical features being encountered. All six patients were in gross heart failure, five of them having auricular fibrillation. Haemoptysis was a feature in all, and the problem is posed

whether the fever is attributable to inflammation associated with areas of pulmonary infarction. One patient tentatively diagnosed as having bacterial endocarditis together with gross heart failure from tight mitral stenosis had fever which failed to respond to antibiotics and failure was intractable; post-mortem examination showed no evidence of bacterial endocarditis. Where doubt exists it is obvious, however, that antibiotics must be given.

Discussion

Any attempt to reduce the incidence of bacterial endocarditis involves the recognition of those with heart disease, and the awareness and control of processes leading to bacteraemia in such patients. The high proportion of patients in the present series who were aware that they had an abnormal heart or who would have given a history of rheumatic fever is of interest and shows the value of simple questioning.

Examination usually reveals obvious valvular abnormality, but the occurrence of endocarditis in the absence of a heart murmur has been emphasized by MacGregor (1956). The so-called innocent apical systolic murmur can be particularly difficult, and may be associated with bacterial endocarditis as recorded in the present series. One of these patients, before the onset of his bacterial endocarditis, had been confidently diagnosed as having such a murmur, and a phonocardiographic recording of it had appeared in a textbook as an illustration of an innocent murmur.

The risk of infection following surgery is a hazard for those with abnormal heart valves, and many cases are recorded—for example, following cardiac catheterization (Winchell, 1953), after cardiac surgery (Fleming and Seal, 1955; Andreassen and Jensen, 1956), while Merritt (1951) recorded an incidence of eight cases of endocarditis, seven of them due to *Str. faecalis* following 7,000 transurethral prostatic resections, seven of them occurring among the 70 patients with known heart disease. In the present series there are 12 examples of infection from such sources, but it is probable that sepsis associated with teeth is a much more frequent source.

The infrequency of *Str. viridans* endocarditis in the edentulous has been emphasized (Hobson and Juel-Jensen, 1956), and this is borne out by the present series. But to argue thereby that patients who have once had bacterial endocarditis should be rendered edentulous is a programme of despair which might logically be extended to include all patients with congenital or acquired valvular heart disease. Davies (1957) recorded a well-documented case of a *Str. viridans* infection in an edentulous patient. In addition, if the ulcer resulting from ill-fitting dentures be accepted as the cause of the *Str. viridans* infection in one of the cases here recorded, then even wholesale extraction will not suffice. Rather it is advocated that a much higher standard of observation and of dental care should be instituted. The necessary standard means that dentists should ask simple questions regarding heart disease and rheumatic fever before extracting teeth in their patients; that all patients known to be at risk should have regular and close dental care; that adequate examination of patients not often seen involves x-ray examination of the teeth; that all extractions in susceptible patients should be performed under antibiotic cover started only just in time to afford adequate blood levels by the time of extraction; that following such extractions, and because antibiotic cover does not always prevent infection, patients should specifically be warned to report early should untoward symptoms arise.

Early diagnosis is obviously of the greatest importance, so that the possibility of bacterial endocarditis must be borne in mind when unusual symptoms in those patients with abnormal hearts are being considered. The possibility of complications of the disease which contribute significantly to its morbidity and mortality constitutes a spur to early diagnosis, for in the present series only 50% of the patients escaped without some more or less unpleasant complication. Wedgwood (1955) has emphasized the delay that often

occurs, and in the series here recorded the high proportion of patients infected for at least three months before diagnosis has already been mentioned, atypical features at the onset of the disease being regarded as contributing largely to such delay.

The recognition of bacterial endocarditis in the elderly is often not considered and may be particularly difficult (Anderson and Staffurth, 1955), for as a rule other conditions are present and cerebral symptoms such as confusion appear more easily. Fig. 4, constructed from the Registrar-

FIG. 4.—Deaths in England and Wales due to bacterial endocarditis: variation with age groups.

General's Statistical Review for England and Wales, illustrates the change in the age distribution of mortality which has occurred since bacterial endocarditis became a curable disease and emphasizes that amongst the higher age groups the greater proportion of fatal cases are now to be found. Because of age trends of the population and the greater ability to control the effects of heart disease, the appearance of bacterial endocarditis in the elderly is likely to remain important.

The treatment of bacterial endocarditis has been reviewed by Beeson (1955), and the *British Medical Journal* (1955) states that, since the M.R.C. trial, change in the form of treatment has been a matter of individual experiment.

In the present series change from three-hourly to six-hourly injections of penicillin has been fully justified, for the large doses at less frequent intervals maintained adequate blood levels equally well. But reduction of the length of treatment is on less certain grounds; for, while it may be adequate for some, unnecessary exposure to risk of relapse for a proportion is unjustifiable. Some of the present series

of patients died from complications of endocarditis at about the time of completion of a six-weeks course of antibiotics adjudged to be curative, and, although no detailed study was made at necropsy concerning the viability of the bacterial colonies seen, their appearance gave no grounds for hope that, in these cases, several weeks less of treatment would have sufficed. In addition a case has already been quoted in which even six weeks was not long enough to effect cure.

For penicillin-sensitive organisms fever that continues despite treatment may be due to systemic reaction to the antibiotic or to inadequate dosage. When considering this latter aspect it must be remembered that, while for streptococci of oral origin the bactericidal and bacteriostatic levels of penicillin are usually very similar, they are not always so, and this may explain failure of otherwise apparently adequate therapy (Berntsen, 1955).

Cure of infection with so-called resistant organisms by the use of bacteriostatic drugs is not to be expected, and a drug or combination of drugs having bactericidal action must be sought (Garrod, 1953). The most generally useful combination at present is penicillin (10 to 20 mega units a day) with streptomycin 2 g. daily. But it is emphasized that treatment of such cases is part of a campaign planned in full co-operation with the bacteriologist, and rapid switching of drugs and dosage schedules merely serves to confuse the issue and may kill the patient. Should sensitivity reactions to the chosen bactericidal drug occur the lethal nature of bacterial endocarditis requires that rapid desensitization should be attempted in preference to reversion to treatment using bacteriostatic antibiotics.

Summary

The results of treatment of bacterial endocarditis from 1945 to 1956 are presented. The immediate mortality has been about 25%. Delay in diagnosis is still considerable, and is discussed. The part played by teeth in the disease is emphasized. So far, there has been a late recurrence rate of some 18%. The disease has its greatest mortality, and is more often missed, among the older age groups.

I am grateful to the medical, surgical, and dental staffs of St. Bartholomew's Hospital for allowing me to follow and report in summary cases treated by them, and to the department of bacteriology, by whose considerable efforts treatment has been guided. This study was started with the encouragement of Professor R. V. Christie and of Dr. G. W. Hayward, who has been kind enough to offer advice, and was continued on the medical unit under Dr. E. F. Scowen. I also wish to express my thanks to Dr. J. E. Cates, who followed cases treated in the first half of the period under review and who facilitated my own work by allowing me access to his records.

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FURTHER STUDIES ON THE TRANSMISSION OF STAPH. AUREUS

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It is now generally assumed that, except for pyogenic infections, the principal reservoir of *Staph. aureus* is the anterior nares of normal humans beings, and that there is a constant passage of this organism from person to person to produce the carrier condition or, when susceptible tissues are available, clinical infection.

The work of Duguid and Wallace (1948) and Hare and Thomas (1956) would suggest that direct transmission from carrier to recipient seldom takes place by means of droplets or droplet nuclei expelled from the nose. An indirect route is more probable, the first step being contamination of the skin and clothing of the carrier. Thence the organisms may reach a recipient who touches the carrier, by carriage on objects such as bedding or towels which have been in close physical contact with the carrier, or by air-borne particles released from his skin or clothing by friction, movement, or washing.

If transmission of *Staph. aureus* occurs in this way the numbers and distribution of the organism on the skin and clothing may govern the ability of the carrier to transmit his organisms to others. Investigation of this forms the first part of our paper. The second part gives details of experiments in which the ability of carriers to transmit their organisms by air-borne particles was assessed.

Experimental Methods

Media.—Isolation of *Staph. aureus* from the nasal cavity, skin, clothing, and air was invariably carried out on nutrient-agar plates containing phenolphthalein diphosphate. Made up in a concentration of 0.5%, it was sterilized by filtration and sufficient added to the melted agar immediately before the plates were poured to give a final concentration of 0.01% (Barber and Kuper, 1951; Hare and Thomas, 1956).

Isolation of *Staph. aureus*.—After incubation for 24 hours on the above medium, the plates were held face downwards over the neck of a bottle of strong ammonia: colonies of *Staph. aureus* turn red, thus enabling counts to be made of the number present. But, since other organisms may produce a similar coloration, representative colonies were invariably purified by plating and identified as *Staph. aureus* only if they were coagulase-positive and microscopically typical.

Contamination of Skin.—This was estimated by rubbing large cotton-wool swabs moistened with broth over an area of approximately 16 sq. cm. at each site. The swabs were immediately rubbed over the whole surface of phenolphthalein diphosphate nutrient-agar plates. With some carriers the whole of each finger was sampled, but with the majority one swab was used for the thumb and all the fingers of each hand.

Contamination of Clothing.—Sweep plates were employed (Blowers and Wallace, 1955) to sample the clothing, each plate being made to traverse the whole length of two adjoining areas on each garment. In the case of the handkerchief, it was bunched up and pressed down on the agar