the two groups owing to the difficulties in making a satisfactory definition.

FIG. 4.—Comparison of survival with different treatments. Corrected survival curve.

Summary

There have been 65 deaths among 132 polycythaemic patients treated with radiophosphorus. These are compared with (1) the normal population, (2) a control series collected from before the isotope era, and (3) a recent series in which cytotoxic drugs were used. The following conclusions are drawn: (1) radiophosphorus-treated patients did not live as long as normal persons; (2) they lived longer than the control patients; (3) radiophosphorus increased the incidence of death from marrow failure; (4) there is no evidence that patients dying

from marrow failure died sooner than those who died from other causes; and (5) the survival rate of patients treated with cytotoxic drugs was slightly less than that of those treated with radiophosphorus.

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Neurological Presentation of Bacterial Endocarditis

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In 1885 Osler described the clinical features of malignant endocarditis, and stated that "a considerable number of cases . . . come under observation . . . for the first time with symptoms of cerebral or even cerebrospinal trouble."

More recent reviews of bacterial endocarditis, though mentioning the incidence of neurological complications, have failed to stress how frequently the latter form the presenting clinical picture. While reviewing cases of bacterial endocarditis seen in this hospital (Hampton and Harrison, 1967) we noted that the initial problem had often been the differential diagnosis of a neurological syndrome.

This paper describes the presenting neurological manifestations in a series of patients with bacterial endocarditis.

Material

The hospital notes of all patients recorded as having bacterial endocarditis between January 1955 and December 1965 were consulted. The diagnosis had been proved at necropsy in 29

cases, by blood cultures in 63 cases, and in 24 cases the patient had been treated on the strength of the clinical evidence. These three groups provided 116 patients for analysis.

Thirty-three patients presented a problem in neurological diagnosis at the time of their hospital admission, and therefore form the basis of this review. In addition, four patients developed neurological complications after their admission.

As the neurological and neurosurgical departments of this hospital serve the regional area, it was possible that a selected series of patients was being studied. However, only 7 of the 33 patients came because of their neurological problem from outside the area of referral of the general medical cases.

Necropsy information was available in 21 of the cases with neurological features.

Results

In 22 patients neurological symptoms were the first feature of their bacterial endocarditis, and in 11 others neurological complaints, though following general symptoms, had nevertheless been the reason for admission to hospital. Thus the diagnostic

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problem presenting on admission had been neurological in approximately a third of the whole group of cases of bacterial endocarditis (33 out of 116). The chief diagnostic problems encountered are shown in Table I.

TABLE I.—Neurological Diagnostic Problems Encountered in 33 Patients Suffering from Bacterial Endocarditis who Presented with Neurological Symptoms

Hemisphere Lesions	17
Established hemiparesis	9
Stuttering hemiparesis	1
Progressive hemiparesis	1
Focal fits	2
Hemianopia	2
Aphasia	2
Brain stem	4
Meninges	7
Meningitis	5
Meningoencephalitis	2
Miscellaneous	5
Thalamic syndrome	1
Headache	1
Grand mal epilepsy	1
Depression	1
Loss of vision in one eye	1

Focal Lesions

In 23 cases the neurological complaints at the time of admission to hospital were attributable to single focal lesions. In 11 of these patients a simple hemiparesis had occurred, and six more had evidence of a hemisphere lesion. Four had symptoms referable to the brain stem or cerebellum. Four complained of visual symptoms, including one who had sustained the sudden loss of sight in one eye owing to a retinal embolus. Ten patients had speech disturbance, including two who had isolated aphasia.

One patient was thought to have a thalamic lesion:

A 53-year-old housewife was first seen in the neurosurgical department. Six months previously she had suddenly become aware of a painful sensation down the whole of the right side of her body. This persisted throughout the rest of her illness. Three months later she had taken an accidental overdose of amyltal in an attempt to control the distressing sensation in her arm and face, and had been admitted to her local hospital. There the murmurs of aortic valve disease were recorded, and she looked unwell. The clinical picture was still dominated by the neurological complaints, and, as at times there was thought to be weakness of the right side, a presumptive diagnosis of cerebral tumour was made. On transfer to the Radcliffe Infirmary she had a slight pyrexia and a tachycardia, and looked unwell. She was obviously distressed by the abnormal sensation down the right side, and this was increased by light touch but not by firm pressure. No objective sensory loss could be demonstrated, nor was there any evidence of altered pain threshold. No pyramidal signs were detected. A left carotid arteriogram was normal. While under observation she developed increasing aortic incompetence and congestive cardiac failure, and haemorrhages appeared in the fundi. Repeated blood cultures were negative, but she was given a total of eight weeks' antibiotic treatment. She died in gross cardiac failure, and at post-mortem examination large vegetations containing bacteria were present on the aortic valve. Multiple cerebral infarctions were found, including a focal thalamic lesion.

Another case was finally diagnosed at operation:

A 27-year-old man with a year's history of ulcerative colitis developed a sudden headache and weakness of the right side of the face with some speech disturbance. This improved over a few days, but 10 days later the headache recurred, this time with weakness of the right arm and then of the right leg. He was admitted to his local hospital, where lumbar puncture revealed a xanthochromic C.S.F. with a normal protein content. Over the next 48 hours he became drowsy, and a further specimen of C.S.F. contained 270 mg. of protein per 100 ml., 165 white cells per cu. mm., and 35 red cells per cu. mm. On transfer to the Radcliffe Infirmary he was drowsy, with marked neck stiffness and a right homonymous hemianopia and hemiparesis. He had an apical systolic murmur and was anaemic (Hb 7.8 g./100 ml.); three blood cultures were sterile. A left carotid arteriogram demonstrated a left middle cerebral aneurysm, and at operation a large intracerebral clot was evacuated and the aneurysm clipped and excised. Penicillin was given postoperatively, and histology subsequently confirmed the clinical diagnosis of a mycotic aneurysm.

A further patient presented with the symptoms of a parietal-lobe lesion:

A 66-year-old woman had been blind for years but could type well. She presented to the neurological outpatient clinic complaining of difficulty in hitting the correct keys on her typewriter. She was found to have a nominal dysphasia, but no other abnormality was detected. Ten days later she was found unconscious in her home. On admission she had improved, but she had a gross nominal dysphasia and a right hemiparesis. While in hospital both femoral and axillary arteries became occluded, and she developed gangrene of the feet and fingers. The heart was thought to be normal; two blood cultures were sterile. She died despite antibiotic treatment, and at post-mortem examination vegetations on the mitral valve were seen along with multiple infarcts in the liver, spleen, and myocardium, and there were many areas of cerebral softening. There was occlusion of both anterior and both middle cerebral arteries.

Meningitis and Meningoencephalitis

Seven patients were thought by the admitting physician to have meningitis or meningoencephalitis, and in five of these the underlying bacterial endocarditis was diagnosed only at necropsy. Three had been thought to have a septic meningitis, one staphylococcal septicaemia, and one virus encephalitis.

Culture of the cerebrospinal fluid was positive in only two cases. In one the same organism was recovered from the C.S.F. and the blood cultures (*Staphylococcus aureus*); in the other, although blood cultures were sterile, *Streptococcus viridans* was grown from the C.S.F.

Post-mortem examination revealed the presence of bacterial vegetations on heart valves, and also provided histological confirmation of the meningitis. Septic cerebral infarctions were also present, but had produced no focal neurological deficit in life.

One patient, thought at first to have a virus encephalitis, was later diagnosed and treated for bacterial endocarditis:

A 19-year-old youth was admitted after an illness lasting 15 days. He had felt unwell with generalized headache and vomiting, and over a period of three days became drowsy and then delirious, with an evening temperature of 104° F. (40° C.). He had then improved spontaneously, but three days before admission had again become delirious, with vomiting and headache. Examination revealed neck stiffness and a positive Kernig's sign, and the optic discs were congested. There were no neurological localizing signs, but the murmur of mitral incompetence was noted. The cerebrospinal fluid protein was 35 mg./100 ml., with a cell count of 60 polymorphs and 10 red cells per cu. mm. In hospital he deteriorated, with a generalized increase in reflexes and the appearance of ankle clonus. He lapsed into deep coma with a right-sided facial weakness. Carotid arteriograms were normal, and an E.E.G. showed diffuse generalized abnormalities. A diagnosis of virus encephalitis was made. Blood cultures were taken, however, and two out of five grew a *Staph. aureus*. He made a good recovery on penicillin, the E.E.G. becoming entirely normal.

Impairment of Consciousness

Although impaired consciousness was noted in seven patients on their arrival in hospital, in only one did it represent the main diagnostic problem. The diagnosis in this one case was subdural haematoma.

Three months before admission a 61-year-old lorry driver had sustained a mild head injury. Three days later he had felt light-headed and had taken to his bed for a few days. Six weeks before admission he developed a cough with green sputum; after three weeks this had not improved, so he was admitted to his local hospital. He was treated with penicillin and discharged. In the next fortnight he became drowsy, confused, and possibly dysphasic, and was incontinent of urine. He was again admitted to hospital, where a C.S.F. protein of 80 mg./100 ml. was found with xanthochromic fluid. He was referred to the neurosurgical department of the Radcliffe Infirmary, where he was found to be drowsy, disorientated, and grossly dysphasic. There was moderate neck stiffness,

with a right hemianopia and hemiparesis. A harsh systolic murmur was heard at the apex. It was thought essential to exclude a subdural haematoma. A left carotid angiogram showed only some irregularity of the vessels, and an air encephalogram showed moderately dilated ventricles. He had a cardiac arrest followed by decerebrate rigidity, and died 48 hours later. At post-mortem examination a large infarct was found in the territory of the left middle cerebral artery, and scattered septic infarcts were present elsewhere. The left middle cerebral artery was full of septic thrombus in which numerous colonies of bacteria were seen. Vegetations were present on the mitral valve.

Mental Symptoms

In six patients mental symptoms were present at the time of admission, and four were admitted in a state of delirium after an illness of less than one week. One patient described visual hallucinations, and another had feelings of unreality. Neurological abnormalities were found on examination in all these patients, and fever was present in all but one. One patient, however, was referred at first to a psychiatric unit for treatment of depression, and no objective neurological deficit was found.

A 45-year-old man had been known to have mitral valve disease for 10 years. Three months before admission he developed a feverish cough with haemoptysis and congestive cardiac failure: all these symptoms responded to treatment. However, he became depressed and withdrawn, and was referred for a psychiatric opinion. On arrival in the psychiatric hospital he was mute and dejected. No abnormality was discovered on examination of the nervous system, but, as he was febrile and had a petechial rash, finger-clubbing, and splenomegaly, he was referred to the Radcliffe Infirmary. A diagnosis of subacute bacterial endocarditis was made and penicillin treatment started. Three days later he collapsed with a spastic tetraplegia, and died shortly afterwards. Necropsy showed the presence of vegetations on a damaged mitral valve. There had been a massive left-sided cerebral haemorrhage.

Headache

Six patients complained of severe headache. In most it was attributed to meningeal irritation or to the occurrence of a cerebral infarction. One patient, however, was admitted specifically for the investigation of headaches.

A 27-year-old man had had migraine for many years with bilateral frontal headache, visual disturbance, and usually right-sided paraesthesiae, hemianopia, and speech disturbance. After dental extractions three weeks before his admission to hospital his headache became generalized and occurred more frequently. There was no longer any associated visual disturbance, and he had become nauseated for the first time. On examination there were no localizing neurological signs. A presumptive diagnosis of a vascular tumour was made, but angiography was normal. An E.E.G. showed a diffuse abnormality. The C.S.F. contained 45 mg. of protein per 100 ml. and no cells. While neurological investigation was being made the murmur of aortic incompetence was noted, and he was occasionally febrile. Blood cultures grew a *Str. viridans*, and he improved rapidly on penicillin treatment.

Fits

Five patients had fits at some stage in their illness, and in three these were the first feature of the bacterial endocarditis. In most cases the attacks had been focal in nature, but no abnormalities could be detected on examination. One patient had generalized attacks.

A 21-year-old man described two attacks of unconsciousness with generalized shaking of the limbs in the previous three months. On examination there were no other neurological symptoms and no neurological abnormalities. He had aortic incompetence and was anaemic (Hb 6.1 g./100 ml.). *Staph. aureus* was cultured from the blood, and after treatment with antibiotics he had no further attacks.

Complications Developing During Hospital Observation

Two patients developed a peripheral neuropathy during antibiotic treatment. Muscle biopsy confirmed a diagnosis of polyarteritis nodosa in one, but was normal in the other. Two further patients sustained a hemiparesis during treatment.

Results of Blood Cultures

Five of the patients had an acute fulminating illness, and in two of these the blood cultures grew a *Staph. aureus*, while in the remaining three the cultures were sterile.

Table II shows the organisms grown from the other cultures. *Str. viridans* and *Staph. aureus* were each recovered from seven cases. In half the cases the cultures were sterile.

TABLE II.—Bacteriological Findings in 33 Cases

Result of Blood Culture	No.
<i>Str. viridans</i>	7
<i>Staph. aureus</i>	7
Micrococci	3
Sterile culture	14
No cultures done	2

Outcome

Information was sought from hospital records, general practitioners' notes, and executive council records on the fate of the 33 patients who had presented with neurological symptoms. Details of the immediate result and clinical status one year later were obtained. In two instances only six months had elapsed since their hospital admission.

Of the 33 patients 22 (67%) died in hospital. One year after discharge two more had died, three were unchanged in their general condition, and six had improved. The cause of death was thought to be the cerebral lesion in nine of the group who died during their stay in hospital. Eight others died of cardiac failure, coronary embolism, or arrhythmia, and in two the terminal clinical picture was that of a septicaemia. One died of gangrene and another of pulmonary embolism.

Post-mortem examination was carried out in 21 of those who died in hospital. The most frequent finding was of cerebral infarction, which was seen in 12 cases and was multiple in nine. The infarcts were simple in seven and suppurative in five cases. Most infarcts were found in the hemispheres (10 cases), but were also seen in the cerebellum, brain stem, thalamus, and spinal cord.

Embolic occlusion of cerebral arteries was present in four patients, and mycotic aneurysms had developed in two others. Histological confirmation of meningitis was obtained in five cases. Massive cerebral haemorrhage had occurred in one patient, and scattered petechial haemorrhages were seen in two others. No cases of subarachnoid haemorrhage were found.

Discussion

Neurological complications occurred in a third of our series of 116 patients with bacterial endocarditis. This incidence parallels that reported by Pankey (1961), but is higher than in most other series (Cates and Christie, 1951; Rabinovich *et al.*, 1965). The possible bias in our source of material has been mentioned above, but can account for only 7 of the 37 cases.

In 33 of the patients the neurological features were the direct cause of hospital admission, and posed the initial diagnostic problem. In 22 cases neurological symptoms preceded all others. At the time of admission to hospital 15 patients presented a differential diagnosis of stroke, seven of meningitis or meningoencephalitis, and six of toxic confusional state or delirium. Others presenting with vertigo, headache, grand mal epilepsy, depression, and impaired consciousness, all proved to have bacterial endocarditis.

Two-thirds of the patients who had strokes were over the age of 50. It is important, therefore, to include the possibility of bacterial endocarditis when considering the differential diagnosis of all patients with strokes.

Even more striking was the diagnostic difficulty encountered in those patients who presented with meningitis or meningoencephalitis. Osler (1885) wrote: "The meningeal complication of endocarditis has not received much attention." A recent case report (Harris, 1965) has also pointed to this association. Our series included seven such patients, in five of whom C.S.F. cultures were sterile. Toone (1941) had noted that bacterial endocarditis should be considered in cases of sterile meningitis. It must also be considered in the differential diagnosis of toxic organic psychoses (Antel *et al.*, 1955), and mental symptoms occurred in 10 of our patients.

In only four patients did their neurological complications develop after antibiotic treatment, and two of these had polyneuritis. This would suggest that the risks of cerebral embolism and meningitic infection are reduced by antibiotic therapy, and further stresses the importance of early diagnosis.

The immediate mortality was high (67%), and was higher than in the cases which had not presented as neurological problems (44%). The difference can probably be attributed to the neurological lesions themselves, and the general features of the bacterial endocarditis did not seem to differ from those seen in cases presenting in other ways. Pearce and Guze (1961) found no difference in cases with or without neurological manifestations.

Two features of the endocarditis were of interest, however. Staphylococci were responsible for a high proportion of cases, and the incidence of staphylococcal infection is higher than in most previous series—for example, Friedberg *et al.* (1961). Staphylococcal endocarditis has been reported to carry a high mortality (Pearce and Guze, 1961), but neurological complica-

tions occurred only rarely in the cases described by Meade (1959). The other striking finding was the high incidence of negative blood cultures, and this general problem has been discussed elsewhere (Hampton and Harrison, 1967).

Summary

The hospital records of 116 patients with bacterial endocarditis have been studied. Thirty-seven showed neurological manifestations, and in 33 these were present at the time of admission to hospital and formed the immediate diagnostic problem. Fifteen presented with strokes, and seven with meningitis or meningoencephalitis. Bacterial endocarditis was unsuspected in five of the seven cases with meningitis, and was discovered only at necropsy.

The importance of bacterial endocarditis in the differential diagnosis of both common and uncommon neurological syndromes is stressed.

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Iron Absorption in Coeliac Disease of Childhood and Adolescence

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Iron-deficiency anaemia is a frequent finding in coeliac disease. The most obvious explanation for the development of this anaemia would be malabsorption of iron. Indeed, malabsorption of iron in idiopathic steatorrhoea of adults has been reported by a number of workers (Badenoch and Callender, 1954; Bonnet *et al.*, 1960; Davis and Badenoch, 1962). There is evidence that idiopathic steatorrhoea of adults and coeliac disease of children are the same hereditary condition (MacDonald *et al.*, 1965). Though a number of radioiron studies in children have been reported (Darby *et al.*, 1947; Sharpe *et al.*, 1950; Schulz and Smith, 1958; Smith, 1964), a study of iron absorption in children or adolescents with coeliac disease has not been found in the literature. The present study of this subject was prompted by the finding, in a few such cases, of iron absorption results within the normal range.

Materials and Methods

Nine children and young adults with proved coeliac disease were studied. Four had been treated by a diet partially or com-

pletely free of gluten at an earlier stage of their illness, but none was receiving dietary or corticosteroid treatment at the time of study. In all these patients the jejunal mucosa was abnormal on both dissecting microscope and histological appearance. Five patients had an excretion of fat in excess of 7 g. per day. All except one showed evidence of iron deficiency with either hypochromic anaemia or low serum iron.

Nine control subjects without steatorrhoea or other evidence of malabsorption were also studied. They were matched as closely as possible with the coeliac group for age, sex, haemoglobin, and serum iron levels. None of the coeliac or other patients had positive tests for occult gastrointestinal bleeding at the time of the iron-absorption test, and none were receiving iron therapy.

Iron absorption was measured by a radioiron balance method. A 3-mg. dose of iron in the form of rabbit haemoglobin was

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