THE SYMPTOMS, DIAGNOSIS AND TREATMENT OF POLYARTERITIS

By R. R. H. LOVELL, M.D., M.R.C.P. and G. A. ROSE, B.M., M.R.C.P.

From the Medical Unit, St. Mary's Hospital, London, W.2

Introduction

Polyarteritis is a disease characterized pathologically by necrosis and inflammation of small or medium-sized arteries. Clinically it produces a constitutional illness associated with local symptoms that result mainly from arterial occlusion. Symptoms may be related to almost any organ but they frequently produce a characteristic clinical pattern. In the absence of treatment the condition is nearly always fatal.

Although the disease was first described by Kussmaul and Maier in 1866, it was rarely diagnosed clinically until about 15 years ago. At the present time about 50 per cent. of diagnoses are made in life. It is certain that this figure could be higher. The condition, though uncommon, is not rare, and its early recognition has become of prime importance since the introduction to therapeutics of cortisone and corticotrophin (ACTH). The immediate effect of these substances on the disease is striking, and although full evidence is still awaited, it seems very probable that, if given soon enough, they may often prolong and sometimes save life.

General Manifestations

Onset. Many patients who develop the disease are already suffering from chronic respiratory infections; others have had recent acute respiratory infections and a few are suffering from polyarthritis clinically indistinguishable from rheumatoid arthritis. The onset can usually be dated to within a few weeks and often to within a few days. Early general symptoms commonly include fever, tachycardia, loss of weight and, in many cases, diffuse aching and tenderness of the limbs. Early local manifestations are most commonly due to involvement of the alimentary tract, joints, peripheral nerves and skin.

Constitutional effects and blood changes. Fever is common but variable; even in the absence of treatment it is liable to sudden exacerbations and remissions. By contrast, tachycardia is generally persistent. Loss of weight tends to be progressive

and severe cachexia may occur. In untreated cases the erythrocyte sedimentation rate (E.S.R.) is almost invariably raised and may exceed 100 mm. in one hour (Westergren). Most patients become anaemic; this is probably due partly to marrow hypoplasia, but gastro-intestinal haemorrhage often contributes to it. Neutrophilia is very frequent. Some degree of eosinophilia is quite common; in cases with lung involvement it tends to be high and may reach a level of several thousands per mm.³. Most patients have abnormalities of the plasma proteins; the globulin tends to be high and the albumin low.

Local Manifestations

Kidney. The kidney is the key organ so far as prognosis is concerned; renal lesions are the commonest cause of death and spontaneous recovery in cases with renal involvement is extremely rare. There are two distinct types of lesion, namely renal polyarteritis, and a characteristic form of glomerulitis which was first clearly recognised by Davson, Ball and Platt (1948); these may occur separately or together. Renal polyarteritis tends to produce cortical infarcts and is usually associated with the presence in the urine of protein, small numbers of red blood cells and sometimes granular and hyaline casts. These abnormalities may only be present intermittently and so repeated examination of the urine is important. In the more severe cases early renal failure occurs and the patient may die in uraemia. Those who survive for longer usually develop hypertension, which is not a feature of the early stages of renal involvement. Once initiated, hypertension is progressive and often ends in the malignant phase. It is a frequent cause of death either during the active phase of the disease or sometimes months or years after active polyarteritis has ceased.

The glomerulitis which may occur in cases of polyarteritis produces an illness with many resemblances to ordinary glomerulonephritis; an acute onset is associated with rapidly progressive renal failure and with the presence in the urine of

protein, numerous red blood cells and cellular casts; sometimes the patient develops oedema. But by contrast with ordinary acute glomerulonephritis the blood pressure remains normal at this stage. A few patients survive the initial phase and these then develop slowly progressive hypertension and renal failure, occasionally with an intervening nephrotic phase.

Heart. Polyarteritis of the coronary arteries usually manifests itself clinically by cardiac enlargement and congestive failure. At necropsy it is common to see numerous infarcts which are usually small, but in life cardiac pain is surprisingly uncommon and the ordinary clinical picture of acute myocardial infarction is rare.

Alimentary tract. The chief symptoms of involvement of the alimentary tract are abdominal pain, which is poorly localized as a rule but sometimes of peptic ulcer type, vomiting, diarrhoea and haemorrhage; the latter may be severe and require transfusion, but more often it shows itself only by the presence of occult blood in the stools. Physical signs in the abdomen are usually scanty. Occasionally the patient may present as a surgical emergency as a result of perforation of the bowel, intra-peritoneal haemorrhage or paralytic ileus. Splenomegaly is infrequent.

Nervous system. Polyarteritis of the vasa nervorum produces a characteristic clinical picture of scattered peripheral nerve lesions. Sometimes the involvement of individual nerves can be distinguished ('mononeuritis multiplex'), but more often the patient presents simply with an asymmetrical polyneuritis. This is sometimes severe and widespread. Cerebral lesions are mostly attributable to hypertension, but local polyarteritis is occasionally responsible for fits, alteration of consciousness or focal lesions.

Skin. The appearances of cutaneous polyarteritis depend upon the depth and size of the affected arteries. Involvement of subcutaneous arteries produces nodules with normal overlying skin. It is commoner, however, to find more superficially placed papules. These tend to appear in crops, usually on the limbs and especially around the ankles. Infarction of the dermis often leads to haemorrhage, vesiculation and central necrosis (Plate 1); the consequent ulcers may enlarge to a diameter of several centimetres (Plate 2). A common feature of cutaneous polyarteritis is the development of a purplish reticulation of the skin (Plate 3); usually this appears where there have first been papules, but sometimes it is the first visible manifestation.

Joints. Joint manifestations, which are common, may be of two types: an acute, transient, sometimes migratory, arthritis, or a more chronic and

deforming lesion which resembles rheumatoid disease.

Lungs. In most cases of polyarteritis the lungs are spared. When pulmonary lesions do occur they precede polyarteritis in other organs, often by months and sometimes by years. Clinically they may produce asthma, a bronchitic type of illness,

PLATE 1

PLATE 2

PLATE 3

or pneumonic consolidation which does not respond to antibiotic therapy. Resultant lung damage may be considerable and lead to fibrosis, bronchiectasis or cavitation. The radiological pattern is very variable; some cases show a crop of coarse miliary foci, others show transient infiltrations of Loeffler's type and others are mistaken for fibrocaseous tuberculosis. Cases with lung involvement tend to show a number of other features which are not characteristic of polyarteritis as a whole; these include high eosinophilia, nasal granulomata and, pathologically, granulomatous polyarteritis and a range of necrotising and granulomatous visceral lesions not demonstrably related to arteries. The term 'eosinophilic polyarteritis' has been suggested for this group of cases (Rose, G. A. 1955).

Diagnosis

Despite the variety of its manifestations, polyarteritis can be diagnosed clinically in most cases. Often it is the diffuseness of the vascular lesions which provides the clue, but in many instances lesions of a single system produce a suggestive or even a diagnostic clinical pattern. In almost all cases there is a raised E.S.R. and tachycardia, and usually also some degree of fever, loss of weight

and neutrophilia. Some of the most characteristic presentations will now be described.

1. One group of patients presents with the symptoms of *hypertension*, either already in the malignant phase or increasing rapidly. Usually in such patients the disease is still active; occasionally it is quiescent, but in this case a history can generally be obtained of an illness months or even years earlier which is compatible with polyarteritis. Sometimes this earlier illness may have attracted little attention at the time and careful history-taking is important.

2. An illness resembling acute *glomerulonephritis* but with a normal blood pressure is suggestive of polyarteritis and should prompt a search for supporting evidence in other systems.

3. The picture of 'mononeuritis multiplex,' or of successive episodes of asymmetrical *peripheral neuritis* is almost pathognomonic.

4. Some cases present with *fever* and have to be distinguished from other causes of prolonged pyrexia.

5. 'Eosinophilic polyarteritis' commences with symptoms of *bronchial* or *pulmonary disease*, generally associated with eosinophilia. A firm diagnosis cannot be made unless or until dissemination of the polyarteritis occurs, but it may be suspected where lung damage is progressive or severe and the eosinophilia is high. It is uncertain how many cases of bronchial asthma with high eosinophilia ($>1,500/\text{mm}^3$) belong in this group, but any such case should be followed up carefully.

6. A diagnosis of polyarteritis should be considered when a patient with *rheumatoid arthritis* develops unexplained lesions in other systems.

Biopsy. Before treatment is started it is of great importance, if possible, to establish the diagnosis by biopsy. Where skin lesions are present these provide the best chance of a positive result, but the lesion selected must be an early one and uncomplicated by necrosis or infection. In the absence of such a lesion a muscle biopsy should be taken. If one muscle is particularly painful or tender this is probably the best site, otherwise pectoral muscle should be chosen since it is vascular and accessible. 'Blind' muscle biopsy offers at least a one in three chance of a positive result. It is important to remove an adequate volume of muscle and general anaesthesia is desirable. When examining either muscle or skin the whole block must be sectioned before a negative report is returned. If the first biopsy is negative, a second and even a third should generally be taken; once cortisone treatment has been started there is little further prospect of a positive result. Provided, however, that there is strong clinical evidence to support the diagnosis, and especially in seriously ill patients or in those with renal involvement,

treatment should be started without awaiting the result of biopsy.

Differential Diagnosis

In many cases an incorrect diagnosis is made because the possibility of polyarteritis is overlooked; once considered, its probability often becomes clear. On other occasions, however, genuine difficulty arises.

The most frequent mistake in the initial stage of the disease is to interpret an acute febrile illness with limb pains as influenza; usually full examination will reveal evidence of local lesions and in any case the course of the disease soon makes the error obvious.

Confusion is possible with a number of prolonged febrile illnesses which produce diverse local lesions. Lymphadenoma without palpable nodes may be hard to distinguish from polyarteritis. Enlargement of the liver and spleen favours the former; cachexia appears earlier in polyarteritis. A mistaken diagnosis of subacute bacterial endocarditis is not uncommon. However, in polyarteritis blood cultures are sterile and there is no response to antibiotics. Disseminated lupus erythematosus can generally be distinguished by its tendency to develop a characteristic rash, to involve serous membranes rather than the parenchyma of organs, to show neutropenia rather than neutrophilia, to show the 'L.E. cell' phenomenon in peripheral blood or bone marrow and to cause exudates in the retina. Cases of polyarteritis with lung infiltrations are sometimes mistaken for tuberculosis (either miliary or fibrocaceous). In general the lesions of pulmonary polyarteritis heal more rapidly than those of tuberculosis and are often migratory, but sometimes the distinction is difficult. The persistent absence of tubercle bacilli from what is often a purulent sputum is a very important observation and the high eosinophilia which is often present in these cases is helpful. In some cases sarcoidosis may need to be included in the differential diagnosis.

The asthma which often accompanies 'eosinophilic polyarteritis' can be distinguished from allergic asthma by the absence of a family history of allergy, by the marked tendency to show high eosinophilia and by the presence of lesions in organs other than the lungs. The relationship between eosinophilic polyarteritis and the range of cases grouped as pulmonary eosinophilia is uncertain; the available evidence does not permit any clear distinctions.

In cases of polyarteritis which present with a picture of acute glomerulonephritis suspicion of the true diagnosis should be aroused by the finding of a normal blood pressure. In cases presenting with malignant hypertension the correct diagnosis is

generally suggested by the associated constitutional illness, evidenced particularly by a high E.S.R. and leucocytosis.

Treatment

Until the introduction of cortisone and ACTH to therapeutics, no known treatment modified the course of polyarteritis. Soon after Hench's discovery of the effect of these drugs on rheumatoid arthritis (Hench and others, 1949), Rose and others (1950) reported their beneficial effect in polyarteritis. From this and subsequent reports it seemed likely that the mode of action of these hormones was similar in both rheumatoid arthritis and polyarteritis; that is, to suppress the inflammatory and necrotic lesions without affecting the causal mechanism.

Our early observations on the response of rheumatoid arthritis to cortisone and ACTH impressed us with the fact that for each individual there is a critical minimal suppressive dose, which is often high, below which there is clear evidence of disease activity and above which there is none (Lovell, 1952). In treating rheumatoid arthritis with cortisone over long periods there is now a tendency to use a dose well below that which completely suppresses the arthritis, thereby lessening the severity of symptoms of cortisone overdosage (Hench and Ward, 1954). Rheumatoid arthritis seldom directly endangers life, and incomplete suppression of symptoms is acceptable. Polyarteritis however is usually fatal, and in treating patients it has seemed reasonable to try to attain a critical dose which will suppress all symptoms.

Some Results of Treatment

In the past five years we have observed eight patients with polyarteritis in whom treatment has been aimed at full suppression of symptoms, the dose of cortisone being limited only so as to avoid intolerable side effects. Details of these cases (patients 1-8) are shown in the Table; two have died, three are in remission and three are alive but still require cortisone.

Both the fatal cases had hypertension when treatment was started and both died in the malignant phase. In Case 1 the blood pressure had risen from 140/90 to 185/115 during the ten weeks before treatment was started. In Case 2 the blood pressure was already 220/110 when he came under observation ten weeks before treatment was started. Active polyarteritic lesions were found at necropsy in Case 1 where treatment had been stopped two months before death. No acute lesions were found in Case 2, who received cortisone until he died.

Two of the three patients who are in remission

TABLE

Patient	Age at Onset	Sex	Biopsy result	Systems mainly involved	B.P. before treatment	Duration of disease before treatment	Treatment and its duration	Outcome
1 T.M.	46	M.	+	Gut, kidneys, nerves	185/115	14 weeks	ACTH 25 mg./day intravenously for three weeks	Died. ACTH stopped two months before death because of malignant hypertension and heart failure.
2 G.B.	58	M.	- (P.M. +)	Nasal mucosa, lungs, kidneys	210/140	? 30 years	Cortisone 100 to 200 mg./day for two months	Died with malignant hypertension.
3 E.H.	47	M.	+	Nerves, kidneys, skin, lungs, heart	135/75	12 weeks	ACTH 25 mg./day intravenously for 16 days	Remission which persists four years after stopping treatment. B.P. now 130/80.
4 A.B.	18	M.	+	Skin, epididymis	120/75	15 weeks	Cortisone 200 to 12.5 mg./day for eight months	Remission which persists one year after stopping treatment. B.P. now 130/75.
5 J.J.	36	M.	+	Skin joints, kidneys	145/90	12 weeks	Cortisone 200 to 12.5 mg./day for 14 months	Remission which persists three months after stopping treatment. B.P. now 130/75.
6 E.S.	33	M.	+	Nerves, skin, kidneys	160/85	24 weeks	Cortisone 200 to 1,000 mg./day for 12 months	Alive. Requires cortisone, 500 mg./day, for suppression of symptoms. B.P. now 210/130.
7 J.C.	18	F.	-	Lungs, skin	110/80	21 months	Cortisone 200 to 500 mg./day or ACTH 120 mg./day for two years	Alive. Requires cortisone, 500 mg./day, or ACTH, 120 mg./day, to suppress asthma. B.P. now 130/90.
8 F.A.	48	F.	+	Skin, joints, muscles	130/80	18 months	Cortisone 200 to 400 mg./day for eight months	Alive. Requires cortisone, 400 mg./day, to suppress symptoms. B.P. now 140/90.
9 J.A.	51	M.	+	Joints, skin	130/75	36 months	ACTH for one month, cortisone 50 to 125 mg./day for 3½ years; 200 to 400 mg./day in last two months	Died. Post-operative pulmonary embolism. B.P. before death 170/120.
10 C.P.	34	F.	+	Lungs, kidney, skin, haemopoietic system	120/75	18 months	ACTH for two months. After interval, cortisone 200 to 50 mg./day for 21 months (50 mg./day for year before death)	Died. Renal failure. B.P. before death 170/120.

after stopping treatment had evidence of renal involvement before treatment was started, as judged, by protein and cells in the urine. None, however, has had hypertension at any stage, and in each case the urine is now normal.

The three patients who still require cortisone or ACTH to suppress their symptoms (after eight months', 12 months' and two years' treatment) present a considerable therapeutic problem. In Case 6 the blood pressure rose within two weeks of starting cortisone and its uncontrolled level is now 210/130. He is receiving pentapyrrolidinium bitartrate ('Ansolsen'). His considerable proteinuria has been unaltered by cortisone in doses up to 1 g. daily, on which dose he became psychotic. During a recent attempt to reduce the dose below 400 mg./day, he developed myocardial infarction, thought to be evidence of recurrent active polyarteritis. Case 7, who was regarded as moribund when treatment was started, and Case 8 are both ambulant. All three patients have gross features of cortisone overdosage.

In addition to these eight patients whose treatment was aimed at full suppression of the disease, two other patients have been treated (Cases 9 and 10 in the Table). Both of these were maintained many months on doses of cortisone which partially relieved their symptoms. Both died.

Case 9 received ACTH initially, then cortisone, 60 to 125 mg./day, for three and a half years. This diminished but did not abolish his polyarthritides and his E.S.R. remained raised. However, having

previously been an invalid for three years, after starting treatment he was able to return to work and to play golf twice a week. He lost no time from work until three months before he died, when he developed very painful ischaemic ulcers round the ankles. These progressed despite increase in cortisone dosage to 400 mg./day. He died from pulmonary embolism ten days after amputation of one leg. His blood pressure rose steadily during the three and a half years of cortisone treatment (Fig.) though at necropsy the kidneys were normal and in life the only evidence of renal involvement was the finding twice of a few red blood cells and once of a few granular casts in 15 examinations of the urine recorded during three and a half years.

Case 10 usually received 50 mg. of cortisone daily. This appeared partially at least to prevent the skin lesions, but she had persistent cough and sputum and gross proteinuria. Nevertheless, from being bedridden at the start of treatment she lived the active life of a housewife for a year before she died of renal failure.

Our experience with cortisone suggests that in adequate dosage it controls dramatically the severe systemic disturbance associated with polyarteritis, reducing the fever, tachycardia and E.S.R. and inducing good appetite and gain in weight. Adequate dosage also appears to suppress the inflammatory and necrotic arterial lesions.

The manifestations of renal involvement may disappear, as in Cases 3 and 5, who appear to have remitted and, so far at least, to have escaped hypertension. However, in Cases 1, 2 and 6 neither the renal lesions nor the hypertension appeared to benefit. It was mentioned that in some untreated cases who die with malignant hypertension, necropsy shows only healed arteritis with renal infarcts. It may be therefore that the key to prognosis with regard to the kidney lies in the extent of renal involvement before treatment begins. Even if, with cortisone treatment, no new lesions develop, the damage to the kidneys which has already occurred may be sufficient to cause hypertension, which can then be modified only by treatment with hypotensive drugs. This emphasizes the urgency of correct diagnosis and prompt treatment and the importance of maintaining full suppression so long as the disease remains active.

Suggested Regime

The dose of cortisone must be chosen individually for each patient. Our recent practice has been to start with 200 mg. daily by mouth in four divided doses and maintain this dose level for at least a week. When there is clinical evidence that the symptoms are controlled, the dose should be reduced by 25 or 50 mg. each week, so long as the symptoms remain completely suppressed, the

FIG.

E.S.R. continues to fall and the urine is free of cells and casts. When a dose of 25 mg./day is reached the final stage of dose reduction should be spread over about six weeks to allow the patient's own adrenal cortex, whose function is diminished by cortisone, to resume its normal activity. Case 4 remitted on such a regime and Case 3 remitted on an even briefer course of intravenous ACTH.

If at the end of the first week there is not clear evidence of control of symptoms, or if at any later stage there is any recurrence of disease activity, the daily dose of cortisone should promptly be raised by at least 100 mg. and it should continue to be raised at intervals of five to seven days, even to 1 g. or more each day, until suppression of the disease is achieved or until the direct effects of cortisone overdosage become intolerable. This circumstance has arisen in only one of our patients (Case 6) who became psychotic on 1 g. of cortisone daily; his mental state was restored to normal by reducing the dose to 500 mg./day.

It will be seen from the table that our surviving but active cases require persistently high doses of cortisone. The outpatient maintenance of patients on such dosage involves much time and trouble, for they are subject to all the well-known hazards of cortisone overdosage (Hench, 1952).

There is as yet no suitable series of untreated patients with which to compare the effects of cortisone treatment. All the eight patients in this series were gravely ill before they received cortisone. Six of them are still alive between eight months and four years after starting treatment; they are all ambulant and three are earning their living. We think it at least very likely that such would not have been the outcome without cortisone. We therefore think that the hardships and hazards of prolonged high cortisone dosage are justifiably endured in managing this disease.

To summarize our views on treatment:

1. Early treatment is vitally important. Severe renal involvement may occur in the disease and the damage caused may be irremediable, leading to death with malignant hypertension.

2. Adequate dosage must be given, namely the dose needed to suppress *all* evidence of activity of the disease. There is no place for partially suppressive therapy such as is used in rheumatoid arthritis.

3. Adequate dosage often means high dosage given for months or years. The physician must therefore be thoroughly familiar with the hazards of cortisone overdosage and must be prepared to supervise his patients closely for a long time.

Summary

The main clinical and diagnostic features of polyarteritis are outlined. The course of the disease is described in ten patients treated with cortisone. A regime of treatment is suggested and problems it entails are discussed.

Acknowledgments

The description of symptoms is based partly on our personal experience and partly on a survey of the natural history of cases of polyarteritis carried out by one of us (G.A.R.) for the Medical Research Council. The survey will be published elsewhere. We are indebted to the Collagen Diseases and Hypersensitivity Panel of the Medical Research Council for permission to quote from experience gained in this survey and to quote six cases treated with cortisone supplied by them. We also thank Dr. W. D. W. Brooks, Professor R. Cruickshank, Dr. J. W. Litchfield and Professor G. W. Pickering for permission to cite cases admitted to St. Mary's Hospital under their care.

BIBLIOGRAPHY

- DAVSON, J., BALL, J., and PLATT, R. (1948), *Quart. J. Med.*, **17**, 175.
 HENCH, P. S. (1952), *Ann. intern. Med.*, **36**, 1.
 HENCH, P. S., KENDALL, E. C., SLOCUMB, C. H., and POLLEY, H. F. (1949), *Proc. Mayo Clin.*, **24**, 181.
 HENCH, P. S., and WARD, L. E. (1954), 'Medical Uses of Cortisone,' Blakiston Co. Inc.
 KUSSMAUL, A., and MAIER, R. (1866), *Dtsch. Archiv. klin. Med.*, **1**, 484.
 LOVELL, R. R. H. (1952), *Postgrad. med. J.*, **28**, 490.
 ROSE, B., PARE, J. A. P., PUMP, K., and STANFORD, R. L. (1950), *Canad. med. Ass. J.*, **62**, 6.
 ROSE, G. A., (1955), in press.

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