Current Practice

Polyarteritis Nodosa

C. T. DOLLERY,* M.D., F.R.C.P.

Brit. med. J., 1969, 1, 827-829

There are few diseases with a more varied clinical picture than polyarteritis nodosa. Any organ may be the first to be affected, and this disease should always be kept in mind in patients who present diagnostic problems, because it can mimic so many other conditions. The aetiology of polyarteritis nodosa is unknown, and diagnosis is complicated by the wide range of other conditions associated with arteritis. These include Wegener's granuloma, lupus erythematosus, rheumatoid arthritis, temporal arteritis, hypersensitivity angiitis, and malignant hypertension. Recently Bywaters¹ described a small group of patients with an illness which had many of the clinical features associated with systemic polyarteritis nodosa but no pathological evidence of arteritis. He named this the "Cheshire Cat Syndrome," because—like the cat in *Alice in Wonderland*, of which only the grin remained—an essential criterion of the disease was missing. Whatever the form of its clinical presentation polyarteritis nodosa usually has a poor prognosis. It is important to make the diagnosis before serious renal damage occurs, because of the possibility that treatment may slow the progression of the disease.

Pathological Features

The disease is characterized by focal necrosis of the wall of small muscular arteries, which begins in the media but almost always involves the internal elastic lamina. The area stains intensely with eosin at the acute stage. The most common complications are thrombosis and aneurysm formation, which may lead to rupture of the vessel. The lesion may heal, leaving only fibrous scars in the vessel wall, but the lumen is often narrowed and the tissue downstream rendered ischaemic. Glomerular lesions with proliferation or fibrosis occur in about one-third of patients with generalized polyarteritis nodosa. Glomerulitis is the preponderant lesion in a group of patients with microscopic polyarteritis nodosa, a condition whose pathological features and clinical course closely resemble glomerulonephritis of the ordinary type.

It is often difficult to obtain biopsy proof of polyarteritis nodosa. Blind biopsy of unaffected voluntary muscle is rarely helpful. It is much better to biopsy an organ or area of tissue which is known to be affected by the disease. If there is evidence of kidney disease a renal biopsy is the most satisfactory way of establishing the diagnosis.

Clinical Syndromes of Polyarteritis

The clinical presentation of polyarteritis is extraordinarily varied, but several patterns recur, and it is helpful to bear them in mind when considering this diagnosis. The disease affects men about twice as frequently as women, and is most common in middle age.

Systemic Illness

The most common presentation is with general ill-health, myalgia, flitting arthralgia, loss of weight, and a fever. The patient usually has a moderate leucocytosis and a high erythrocyte sedimentation rate. In contrast to disseminated lupus erythematosus the gammaglobulin fraction of the plasma proteins is usually not elevated. Such symptoms can be confused with those of any pyrexia of unknown origin. The differential diagnosis between polyarteritis and bacterial endocarditis can be particularly difficult. Of 130 patients with polyarteritis in the Mayo Clinic series² 70% had general systemic symptoms of this kind, though they were often associated with other features.

Pulmonary Disease

Rose and Spencer³ drew special attention to the pulmonary type of polyarteritis nodosa, which they found in 14 of 111 proved cases. These patients presented with asthma or chest infections, and their chest radiographs showed miliary shadowing and irregular areas of consolidation, and four patients had cavities. Most of the patients with pulmonary polyarteritis had eosinophilia, and if their survival was reckoned from the onset of respiratory symptoms they had a better outlook than other patients in the series. However, eventually systemic manifestations of the disease appeared, and if survival was counted from the onset of these symptoms the prognosis was worse than average.

In the Mayo series² 20 of the 130 patients had asthma, and of these 14 had an eosinophil count of 1,500/cu. mm. or more. Survival among the patients with pulmonary manifestations was no better than other patients with the disease. The usefulness of distinguishing the pulmonary type of the disease as a separate entity seems open to doubt. However, polyarteritis nodosa must always be considered in the differential diagnosis of lung shadows accompanied by eosinophilia.

There is some difficulty in distinguishing patients with pulmonary polyarteritis from those with Wegener's granuloma. The necrotic giant cell granuloma described by Wegener affects the middle ear, the nose and air passages, the trachea, or the lung itself.⁴ It is usually accompanied by an arteritis of the small vessels of the kidney, and the clinical course is very similar to polyarteritis nodosa. Some patients present with renal failure and the granuloma is found only after careful search.

Renal Lesions

Polyarteritis causes two types of lesion in the kidney. When the arcuate arteries are affected similar lesions are produced to those found in muscular arteries elsewhere in the body. The patient may present with loin pain, dysuria, or haematuria, but often renal involvement is diagnosed only after a finding of a

* Professor of Clinical Pharmacology, Royal Postgraduate Medical School.

variable degree of proteinuria and microscopic haematuria. The intrarenal arteries affected may be stenosed or occluded, causing renal infarction and scarring. Often the acute necrosis of the arterial wall heals, leaving a fibrous scar or an aneurysm. Such patients often develop accelerated hypertension later in their clinical course, but the arteritic lesions precede the rise of blood pressure.

Involvement of the small vessels and glomeruli of the kidney produces a microscopic form of polyarteritis which can give rise to acute renal failure and an illness which closely resembles post-streptococcal glomerulonephritis. The kidneys are enlarged and pale, and the glomeruli show patchy fibrinoid necrosis, epithelial crescents, and focal fibrosis.⁵ Small thrombi are present in some glomerular capillaries. Some glomeruli may be spared, and the picture resembles a focal embolic nephritis. Some pathologists do not accept that this condition can be distinguished from post-streptococcal glomerulonephritis on the basis of the renal lesions alone. However, most patients with microscopic polyarteritis nodosa are older than patients with classical glomerulonephritis and have other features of polyarteritis. Hypertension is not so common an early feature of microscopic polyarteritis as it is of glomerulonephritis, but eventually severe hypertension develops in most cases. Death in uraemia is the usual outcome.

Neurological Lesions

Polyarteritis nodosa may involve any part of the nervous system. Patients may present with either stroke or coma. However, arteritis involving peripheral nerves is more common, and this may be the first indication that an obscure febrile illness is polyarteritis. In the Mayo series² 68 of 130 patients had mononeuritis multiplex at some stage of their illness. Muscle wasting and weakness—for example, foot drop—loss of reflexes, and sensory impairment are irregularly distributed according to the nerves involved. In some cases peripheral nerve trunks may be palpable and tender.

Other Manifestations

A wide variety of abnormalities of the skin can occur in polyarteritis. They include urticaria, petechiae, ecchymoses, papules, nodules, bullae, vesicles, and necrotic ulceration.⁶ Usually the diagnosis will be suggested by other clinical features of the illness, but biopsy may be helpful.

Polyarteritis nodosa often involves the gut. Symptoms range from occasional plain or colic to an "acute abdomen," with necrosis of a segment of small bowel following occlusion of its feeding vessel. Acute ulceration of the gut and severe gastrointestinal bleeding may also occur. Hepatitis, pancreatitis, and testicular lesions are less common presentations.

Associated Diseases

Rheumatoid arthritis and disseminated lupus erythematosus are the conditions most likely to be confused with polyarteritis nodosa. Moskowitz's necropsy series⁷ of 56 patients with polyarteritis included four patients with lupus erythematosus and five with rheumatoid arthritis. In general the arteritis associated with rheumatoid arthritis is a subacute or chronic granulomatous inflammation with relatively little necrosis. Occasionally, however, the clinical and pathological manifestations are very similar in polyarteritis nodosa and rheumatoid arthritis.^{8,9} L.E. cells are more likely to be present if there is necrotizing arteritis.¹⁰ It must be accepted that in some patients no meaningful distinction can be made between these various disease entities.

Pathogenesis

There is no evidence concerning the aetiology of polyarteritis nodosa in man. Many workers have suggested that polyarteritis nodosa is a manifestation of hypersensitivity. It is possible to produce an arteritis by injecting foreign serum in hypersensitive animals, but most pathologists are now agreed that the lesions so produced do not very closely resemble polyarteritis nodosa.¹¹ Rich¹² has been a strong protagonist of the view that polyarteritis nodosa is related to hypersensitivity, and has suggested that sensitivity to sulphonamides may be important. However, a recently reported series of patients with polyarteritis nodosa showed only a small proportion who have ever been treated with sulphonamides. There is no increase in gammaglobulin in the serum of patients with polyarteritis and no real evidence that the human disease is autoimmune. Recently Roge¹³ has produced polyarteritis in rabbits by intraperitoneal injection of the serum of a patient with acute polyarteritis nodosa. Serum from patients with polyarteritis nodosa in remission had no effect. This observation has not yet been confirmed by other workers.

Prognosis

Until comparatively recently polyarteritis was a diagnosis usually made at necropsy. It is not surprising that early reports show an extremely poor prognosis. Rose and Spencer³ found a survival of about 10% at five years among patients with no pulmonary involvement. Among those with pulmonary involvement there was a 25% five-year survival from the onset of respiratory illness but only a 4% five-year survival from the onset of systemic manifestations of the disease. In 1967, Frohnert and Sheps² found a considerably better prognosis. Among patients who had received intensive steroid treatment there was a 48% five-year survival. Hypertension and renal disease both reduced the survival to about 34% at five years. A small number of patients may show permanent healing of polyarteritis, but the usual course is a progressive deterioration to death in uraemia, cerebral or myocardial infarction, or haemorrhage from a ruptured aneurysm.

Treatment

The use of corticosteroids in high doses can produce a dramatic clinical improvement in a patient with systemic manifestations of polyarteritis nodosa. Well-being and appetite improve, fever and erythrocyte sedimentation rate decline. The influence of steroids on long-term prognosis is disputed. Frohnert and Sheps² found a 48% five-year survival among patients treated intensively with steroids and only 12.7% five-year survival among those who had received no steroid treatment. The M.R.C. study published in 1960¹⁴ showed a 62% survival at three years among patients treated with steroids and 37% among a group of patients who were not treated. However, neither study was carried out as a controlled therapeutic trial, and in the M.R.C. study there were many more patients with hypertension among the untreated group. When these were removed the apparent advantage among the treated patients disappeared.

Steroids in high doses are often employed to suppress the systemic manifestations of the disease, but further evidence is needed before any definite statement can be made about their effect on prognosis. If prognosis is improved by steroids the effect is probably small.

Immunosuppressive drugs such as azathioprine have been used in a few cases of polyarteritis nodosa and improvement has been claimed. The evidence available is not adequate to permit any conclusion.

REFERENCES

- ¹ Bywaters, E. G. L., *Postgrad. med. J.*, 1968, 44, 19.
- ² Frohnert, P. P., and Sheps, S. G., *Amer. J. Med.*, 1967, 43, 8.
- ³ Rose, G. A., and Spencer, H., *Quart. J. Med.*, 1957, 26, 43.
- ⁴ Walton, E. W., *Brit. med. J.*, 1958, 2, 265.
- ⁵ Davson, J., Ball, J., and Platt, R., *Quart. J. Med.*, 1948, 17, 175.
- ⁶ Winkelman, R. K., and Ditto, W. B., *Medicine (Baltimore)*, 1964, 43, 59.
- ⁷ Moskowitz, R. W., Baggenstoss, A. H., and Slocumb, C. H., *Proc. Mayo Clin.*, 1963, 38, 345.
- ⁸ *Brit. med. J.*, 1966, 1, 1027.
- ⁹ Kulka, J. P., *Bull. rheum. Dis.*, 1959, 10, 201.
- ¹⁰ Schmid, F. R., Cooper, N. S., Ziff, M., and McEwen, C., *Amer. J. Med.*, 1961, 30, 56.
- ¹¹ Zeek, P. M., *Amer. J. clin. Path.*, 1952, 22, 777.
- ¹² Rich, A. R., *Bull. Johns Hopkins Hosp.*, 1942, 71, 123.
- ¹³ Rogé, J., Martin, E., Crozier, J. A., and Pierre-Bourgeois, *Sem. Hôp. Paris*, 1965, 41, 3087.
- ¹⁴ M.R.C. Study on Treatment of Polyarteritis Nodosa with Cortisone: Results after Three Years, *Brit. med. J.*, 1960, 1, 1399.

TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in common use.

Oral Hypoglycaemic Drugs

The search for oral hypoglycaemic drugs preceded the discovery of insulin, but the development of the latter compound took the initial impetus from the manufacture of suitable guanide derivatives, and after early adverse experience with Synthalin these compounds were not revived until the biguanide, phenformin, was used in clinical trials in 1957.

The discovery of the sulphonylurea drugs, on the other hand, followed a chance observation by Janbon and his colleagues¹ that a sulphonamide might reduce blood sugar levels in experimental animals. This led to the development of a series of substances with the SO₂NH-grouping, which is also found in the sulphonamides and in many of the currently used oral diuretics.

Recent research into the physiological disturbances of diabetes has been advanced by the availability of methods for the measurement of plasma insulin levels and by greater knowledge of the disorders of metabolism, usually not detected without special investigation, that occur in obesity and both latent and overt maturity-onset diabetes. In the light of this new knowledge, some of the modes of action of both the sulphonylureas and the biguanides can be explained, and both groups of drugs have proved to have a place not only in clinical practice but also in the research laboratory.

Sulphonylurea Drugs

These include chlorpropamide, tolbutamide, acetohexamide, and tolazamide. A closely related compound, glymidine, is also available. All are effective by mouth, well absorbed, and strongly bound to protein in the plasma.

Mode of Action.—Shortly after the first report by Janbon it was shown that this group of hypoglycaemic agents is effective only in animals possessing pancreatic function.² This led to the generally accepted view that the sulphonylureas stimulate the pancreatic beta-cells to produce greater amounts of insulin and thereby lower blood sugar levels in diabetic patients. This may be an over-simplification, and, in addition, these drugs may potentiate the effect of insulin at peripheral tissue sites.³

Metabolism.—The principal differences between compounds in this group lie in their rates of metabolism and elimination from the body. *Tolbutamide* has a metabolic half-life of between four and five hours, is rapidly converted to inert carboxy-tolbutamide in the liver, and is excreted by the kidneys in this form. The excretion product may produce a flocculent precipitate if acid is added to the urine, and may be confused, therefore, with urinary protein if the sulphosalicylic acid test

is used. The maximum effect of oral tolbutamide on blood sugar levels occurs between four and six hours after its administration, and, because the compound is metabolized and excreted rapidly, it is given in divided doses, usually three times a day.

Chlorpropamide, on the other hand, is hardly altered by its passage through the body, less than 1% being metabolized. It is excreted by the kidney and has a half-life in the body of about 36 hours. As it is strongly bound to protein it may take 10–14 days before it is finally eliminated from the body after administration has been stopped, and during this period it is capable of exerting a hypoglycaemic effect. It is given as a single daily dose, but response to alteration of dose will be relatively slow, and in the event of hypoglycaemia the reaction may be more difficult to reverse.

The duration of effect of the other sulphonylureas lies between these two extremes.

Indications

Sulphonylureas are used most appropriately in the management of maturity-onset (or "ketoacidosis-resistant") diabetics who have not responded to dietary regulation alone. Typically, these will be obese patients with high plasma insulin levels and little tendency to develop ketosis. Dietary control must still be a priority in their management, and the temptation to abandon diet in favour of control by tablet alone should be resisted. Indeed, gain in weight is a common accompaniment of treatment with the sulphonylureas. Many elderly diabetics receiving oral hypoglycaemic drugs could be controlled by diet alone.

There is seldom any place for the use of sulphonylureas alone in young diabetics, and these drugs are contraindicated in any form of diabetic crisis such as ketosis, infection with increasing glycosuria, or surgical emergencies. The close control demanded in the management of the pregnant diabetic makes pregnancy a further contraindication.

The most difficult decision arises in the small group of adult diabetics, often presenting in their middle thirties, who respond well to oral agents at first. Experience from several clinics suggests that these patients commonly lose their initial response and require successively a change of sulphonylurea, combined treatment with a biguanide, and, ultimately, a change to insulin.

Recent figures from a large diabetic clinic indicate that, overall, approximately 37% of the patients require insulin, 38% are controlled by diet alone, and 25% are controlled by diet and oral hypoglycaemic drugs. However, initial success with sulphonylureas is often followed by "secondary failure." Any attempt to estimate the frequency of this from the published reports is fraught with difficulty, as few authors accept a