POLYARTERITIS NODOSA
Report of a Case

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Credit is usually given to Kussmaul and Maier for the description of periarteritis nodosa in 1866. The cases were originally suspected to be suffering from trichinosis. However, it is of historical interest that Rokitansky first described the macroscopical lesions in 1852 under the title “The formation of aneurysms of the arteries in general, except the aorta and most of its primary branches, with a further exception of the cerebral arteries.” Thirty-five years later Eppinger reviewed the microscopical sections and confirmed the diagnosis. There is even some reason for believing that the disease was recognized as early as 1755 by Michaelis and Matani; and in 1810 Pellet an reported briefly a case in which he counted 63 small aneurysms of various arteries. Carnegie Dickson pointed out that, since the disease involves the arteries of almost any part of the body and since the pathological changes are not confined to the adventitia, a more appropriate name for the condition would be polyarteritis nodosa and that name has now been generally accepted.

Polyarteritis nodosa is still considered to be a very rare complaint although a considerable number of cases have been reported within the last ten years. The symptoms produced are diverse and it has been suggested that the condition may be a pathological entity rather than a disease sui generis. The order of frequency of the more significant findings is: fever, leucocytosis (10,000–54,000 per c.mm.), albuminuria, hypertension, rapid onset of symptoms, abdominal pain, oedema, loss of weight, haematuria and neuritis. Tonkin and Pulvertaft (1948) emphasized that palpable skin nodules and eosinophilia, usually regarded as essential diagnostic criteria of polyarteritis nodosa, are very rarely encountered, and Handley and Martin (1939) found that only some 12 per cent of the reported cases showed a marked eosinophilia and noted figures sometimes as high as 77 per cent of 20,000 cells. Much more constant features of the disease are persistent tachycardia out of proportion to the fever, cardiac arrhythmia and a changing electrocardiogram. These points are especially striking in the so-called “cardiac type” of the disease. I would like to add a rather high erythrocyte sedimentation rate, the absence of response to digitalis therapy and persistent signs of severe myocardial involvement, manifested
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by pulsus alternans and gallop rhythm. Another clinically important sign may be the complete unawareness by the patient of the gravity of his condition. Where the nervous system is involved the presenting symptoms may be those of multiple interstitial neuritis with degeneration of the peripheral nerves secondary to the damage to the nutrient arteries rather than those of toxic polyniuritis. Similar lesions may occur in the brain and spinal cord and the spinal fluid may be under increased pressure. There may be xanthochromia and a polymorphonuclear leucocytosis. Bearing in mind these signs and symptoms should assist in the diagnosis of the disease during life or at least lead to its consideration in a differential diagnosis. However, a comparatively small number of cases have been diagnosed during life with the exception of the "nodular type" where the diagnosis is usually established by biopsy. The difficulties can easily be understood if one considers how widespread and profuse are the lesions found at autopsy.

The histological changes suggest a necrotizing arteritis and the location of the lesion in the vessels depends upon the size of the artery. In larger arteries changes occur at the junction of the media and adventitia, in the small vessels the lesions are subintimal. Arkin (1930) has divided the process of the disease into four stages. The first stage is dominated by necrotic changes in the inner media of the arterioles and in the outer media of the larger arteries. Öedema and fibrinous exudate are also present. In the second stage exudative inflammation is predominant and the media and the adventitia are the seat of massive accumulations of polymorphonuclear cells, eosinophilic leucocytes, lymphocytes and plasma cells. Proliferation of connective tissue occurs in the intima, and complications such as formation of aneurysms, thrombosis and haemorrhages occur towards the end of this stage. In the third stage the regenerative and proliferative process are predominant. Organization of thrombi and formation of granulation tissue take place. The final stage is characterized by formation of scar tissue and healing. In an advanced case hardly a single organ escapes although more recently it has been stated that in a significant number of cases the pathological changes can be demonstrated only after careful microscopical examination of every organ and that the disease may be localized to one organ only.

Contrary to the belief that polyarteritis nodosa carries a 100 per cent mortality "healed cases of polyarteritis nodosa" have recently been reported, and Tonkin and Pulvertaft (1948) in their report of a case state that over half the patients recover and this recovery may even include complete resolution of the pathological lesions in the arteries. Although this figure of 50 per cent recovery strikes one as rather high it may include cases where the disease runs an intermittent course for many years.

Consideration of the fact that the lesions of polyarteritis nodosa can be localized leads to speculation as to whether temporal arteritis can be considered a variant of the same disease. It is true that temporal arteritis is more often found in older people but the reported range of age in cases of polyarteritis nodosa is extending from 3 months to 78 years (Keith and Baggenstoss, 1941).
Acute temporal arteritis has been mentioned in the literature since 1931. There is considerable similarity between the cases. Some patients often present the appearance of being severely ill entirely out of proportion to the amount of local disease present. Hoyt, Perera and Kauvar (1941) believe that temporal arteritis is but a local manifestation of a more widespread disease. The fact that the pathological specimens demonstrate very similar histological changes to the findings in polyarteritis nodosa leads one to suspect that it is a localized form of the latter disorder. Gordon and Thurber (1946) reported a case of temporal arteritis occurring in a 65-year-old man who complained of severe headache, pain over both temporal regions and severe pain in both thighs. Biopsy of the tender pulsating arteries revealed active arteritis. The authors feel that the pain in the thighs was part of the clinical picture and that temporal arteritis is really only a part of widespread polyarteritis. Furthermore, if one compares the findings in temporal arteritis with reports of necropsy examinations in polyarteritis nodosa one feels inclined to subscribe to this view as many arteries exhibit the same pathological changes as do the temporal arteries and the histological pictures are similar in both diseases.

Theories as to causation of polyarteritis nodosa fall mainly into two groups:

(a) Infection—(*Spirochæta pallida*, streptococcus, virus, parasite).
(b) Allergy—(allergic reaction to a variety of toxins, including organic arsenicals, sulphonamides and thiouracil).

None of these theories could conclusively be confirmed so far. The histological appearance in a number of cases strongly suggested the type of reaction occurring in the vessels in the rickettsial diseases but all attempts with appropriate stains, however, have failed to reveal rickettsial bodies. Some authors thought of the possibility that, in certain instances, a rheumatic infection acts as a sensitizing factor and prepares the way for the destructive attack by the infective agent of polyarteritis nodosa. Cohen, Kline and Young (1936) believe that polyarteritis nodosa is a manifestation of clinical allergy so severe that irreversible and destructive lesions occur in the arterial walls and lead to disturbances in function of the organs supplied by the involved vessels. They consider every patient with severe allergy as a potential candidate for polyarteritis nodosa. Others thought of a hyperergic defensive reaction of the small arteries and arterioles to a variety of toxic and infectious factors. This belief receives support by the frequency with which preceding or concomitant infections are seen in cases of polyarteritis nodosa. It has further been suggested that many of the unexplained fibrosed or recanalized blood vessels which, in the past, have been encountered in routine post-mortem examinations and biopsies, and which have been previously brushed aside for want of explanation, may have been healed lesions of polyarteritis nodosa of varying degree, caused by various agents which had existed as localized lesions or which had remained unrecognized during life. Rich (1942) reported a series of cases in which typical, fresh lesions of polyarteritis nodosa were found in patients who came to autopsy shortly after having had serum sickness or hypersensitive reactions to
sulphonamides. A typical diffuse polyarteritis nodosa had been produced experimentally by establishing a condition analogous to serum sickness in men. Rich and Gregory (1943) claim to have demonstrated that polyarteritis nodosa is one manifestation of the anaphylactic type of hypersensitivity and they came to the conclusion that widely different types of sensitizing antigens are capable of causing polyarteritis nodosa in men. This view seems to be supported by the frequent coincidence of asthma and polyarteritis nodosa.

**CASE RECORDS**

C.Q.M.S. "X," aged 37, was first seen in the outpatient department of a military hospital in July 1948 and he was admitted a few days later. He looked ill and complained of general malaise, weakness, slight cough; abdominal pain, anorexia, sweating and loss of weight.

*History.*—He had always enjoyed good health. Three months ago he developed a number of small boils on trunk and limbs. A diagnosis of impetigo was made and the treatment consisted of two injections of penicillin and local applications of penicillin ointment. The condition improved, but the skin lesions never subsided completely and occasionally new eruptions developed. He stated that five weeks prior to admission he thought he caught a cold which left him with a persistent cough and some shortness of breath. Two weeks later he was suddenly seized by a very sharp pain in the "stomach" after he had a few drinks. He felt sick but he could not vomit. This pain was localized in the right hypochondrium and epigastrium and had persisted, more or less, ever since its first onset. It had varied in intensity and seemed not to be related to meals. He thought his cough had improved since the abdominal pain had developed and he had lost over 1 stone within the preceding two months. There were no other abnormal symptoms.

*Examination.*—Rather thin, pale and ill looking man. Temperature 99, pulse regular, rate 100 per minute, respirations 26. Skin: scattered septic lesions on trunk and extremities, most of them localized on forearms, fingers and lower limbs. Some were fresh, others were covered by crusts. A few were slightly infiltrated and tender. There was evidence of healed lesions on the trunk in the form of scars and brownish pigmentation. No subcutaneous nodules palpable. No adenopathy, no clubbing of fingers, trachea central. Lungs: hyperresonant, bilateral basal crepitations. Heart: apex beat in 6th intercostal space, 3-8 cm. outside mid-clavicular line, no murmurs, pulse regular, normal volume, equal, rate 100 per minute, blood pressure 165/110, neck veins not distended. Abdomen: liver enlarged (two fingerbreadths), tender, marked tenderness in the epigastrium, spleen not palpable, no evidence of ascites, no abdominal tumour palpable. Examination per rectum: n.a.d. Central nervous system: n.a.d. Fundi: no retinopathy. Limbs: no oedema. Urine: massive albumin, no frank hematuria.

On the day of admission, three days after he had been seen in the outpatients clinic, he suddenly developed acute pulmonary oedema. There was now tachypnoea, orthopnoea, profuse sweating, ashen-grey pallor, anxiety, cough with slightly blood-stained frothy sputum, pulse irregular, soft, rate 160 per minute approx., blood pressure 180/120, temperature 101°. On examination there were moist coarse râles over both lungs extending up towards both clavicles, the liver was now much more enlarged and tender and its edge could be felt in the region of the umbilicus. There was evidence of sacral oedema and slight swelling of both ankles.

*Progress.*—The emergency treatment consisted of morphine, atropine, and mersalyl. Digoxin 0-5 mg. was injected intravenously. All signs and symptoms of pulmonary oedema subsided within a few hours but the tachycardia persisted and the pulse remained elevated between 120 and 130 per min. in spite of continuing treatment with digoxin per mouth. The blood pressure did not fall below 165/110 and the
temperature varied between 99.2°–101.4°. The general condition of the patient, however, improved and his abdominal pain subsided. Later pulsus alternans, frequent extrasystoles and gallop-rhythm developed and digoxin had to be reduced and eventually discontinued. As the temperature occasionally rose to 102° and as more septic skin lesions developed a large course of penicillin was decided upon and a prolonged course, extending over six weeks, was commenced, a total dosage of 20 million units being given by intramuscular injections. In the course of this the temperature became normal and the skin lesions subsided. The tachycardia persisted, however, and a rough systolic murmur—which was loudest medial to the apex beat—developed. The urine continued to show albumen and occasionally red blood cells and signs of increasing myocardial involvement became more and more marked clinically and by repeated electrocardiograms. The patient died of heart failure, seven weeks after admission.

INVESTIGATIONS

Blood: W.B.C. 10,500 per c.mm. - 12,500 (75 per cent polymorphs), no eosinophilia, Hb. 70 per cent (Sahli), R.B.C. 3,500,000 per c.mm., blood urea 40 - 60 mg. per ml., E.S.R. 97 - 109 mm. in one hour (Westergren), repeated blood cultures sterile, W.R. and Kahn negative.

Sputum: No acid-fast bacilli seen, no predominant organism in repeated examinations of specimen.

Urine: Persistent heavy albuminuria, occasionally red cells, no casts seen, culture sterile.

Electrocardiograms: Three tracings were taken during the course of the illness and a constant change was observed. All of them suggested left axis deviation and severe myocardial involvement. The first electrocardiogram, taken soon after admission, showed changes of T and S-T in lead 1, 2, and 4 (precordial lead) suggesting involvement of the myocardium of the anterior wall of the left ventricle (fig. 1A), while fig. 1B and fig. 1C revealed notching and broadening of the QRS-complexes, suggesting bundle branch block. All these changes, however, could be interpreted as digitalis effects.

X-rays of Chest: At first showed acute pulmonary oedema and enlargement of heart. Six days later, showed the response to treatment and the subsidence of pulmonary oedema.

POST MORTEM

Heart: Pericardial sac dilated, containing 80 c.c. of clear, yellowish fluid. Pericardium translucent, no adhesions. Heart: weight 500 grammes. Generalized enlargement, the apex formed by the markedly hypertrophied left ventricle. Coronary arteries straightened, along the lines of the vessels all branches show small nodules, grey and greyish red in colour resembling chains of small pearls, sharply defined and appearing to be multiple small aneurysms (fig. 3). These are particularly well seen on the posterior wall and on the margo acutus. The descending branch of the right coronary artery shows a double row of these nodules and they are also seen on the branches of the left coronary artery, but with multiple smaller milliary and submiliary nodules, some hardly recognizable macroscopically, on their branches. There was no evidence of hyperämia. All cavities of the heart dilated and their muscular walls hypertrophied. Right ventricle at conus pulmonalis 6 mm. in thickness, with trabeculae round and large. Left ventricle, thickness 18 mm., myocardium stiff and firm, no evidence of ischemic infarcts or scars. Endocardium normal, all valves normal. The lumen of the descending branch of the left coronary artery is not obstructed and the above described nodules appear not to originate from the main branch, but seem to be nodular thickened walls of the smaller branches. The aorta is narrow and elastic, only very slight thickening of the intima in its lower parts can be seen. The intercostal arteries are affected in a similar way as the described coronary arteries.
Fig. 1.—Electrocardiograms showing left axis deviation and myocardial changes.

A. One week after admission. Changes suggest TI type infarction.
B. Three weeks later. Widening of QRS Complexes suggesting branch block.
C. Two weeks before death. Low voltage in lead 2, bundle branch block.
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**Fig. 2.**—Posterior wall of heart showing descending branch of right coronary artery with nodules along the vessel.

*Peritoneal Cavity:* Contained 250 c.c. of yellowish clear fluid. No adhesions. The serous membrane of the stomach and of the intestines show multiple small greyish-white nodules on the lines of the branches of the mesenteric arteries.

*Liver:* Weight 1,830 grammes. Some small, irregular, greyish-red areas which proved to be haemorrhagic infarcts on cut surface. The branches of the hepatic artery show the same nodular lesions as described above. The lumen of the nodules is either narrowed or thrombosed. Gall-bladder and ducts normal.

*Spleen:* Weight 190 grammes, firm and smooth. The vessels show small nodules macroscopically.

*Pancreas:* N.A.D.

*Suprarenal Glands:* Small, the cortex decreased, brown, with lipoid considerably diminished.

*Kidneys:* Right kidney: weight 160 grammes. Left kidney: weight 150 grammes. Both organs stiff, the capsule difficult to strip. The surface of both kidneys shows a number of dark greyish-red fields, some of them sunken, others elevated. The cut surface shows multiple grey, miliary nodules.

*Urogenital Tract:* Macroscopically n.a.d.

**Histological Examination**

*Heart:* Sections of the wall of the right ventricle and auricle show several small branches of the coronary arteries with circumscribed nodules and aneurysmal dilatations. The wall of the vessels is considerably thickened, there is fibrinoid necrosis, the structure of all membranes of the vessels is indistinct, the elastica and muscularis is destroyed and there is a marked inflammatory infiltration of all layers including the
adventitia. In some areas the vessel wall cannot be recognized and is replaced by a fibrous tissue with round cells and many newly formed vessels of the type of giant capillaries. In the adventitia small round cells seen, mostly plasma cells. The “elastica interna” can only be recognized with great difficulty. The intima is considerably thickened everywhere and the lumen is narrowed or partly obliterated by the changes in the internal membrane. In some areas the lumen is obstructed by thrombi which are fresh, organized or in the state of recanalization. Many newly formed giant capillaries are seen in these thrombi. The myocardium shows considerable hypertrophy of the muscle fibres. The nuclei are very big and irregularly shaped. In the ventricular wall only a few small infarcts are seen. The auricular wall shows larger areas of fibrous tissue, which have only a few nuclei and are situated between the muscle fibres (fig. 3).

**Brain:** Considerable venous congestion in the cortex of the left frontal lobe. Small areas of softening with destruction of the nervous tissue.

**Liver:** Considerable venous hyperæmia and oedema. The branches of the hepatic artery show changes similar to those seen in the coronary arteries.

**Kidneys:** Arterial lesions similar to those described previously. The cortex shows small fields of scar tissue but no fresh ischaemic necrosis. The glomeruli partly hypertrophic and congested. Frequent periglomerular infiltration of round cells. Here the venous hyperæmia is also considerable.

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**Fig. 3.—Section showing myocardium with hypertrophy of muscle fibres and fibrosis.**
The vessels are thickened showing thrombi some obliterating the lumen. (Low power.)

Magnification 100 approx.
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Spleen: Hyperplasia of the follicles and pulp. No arterial changes seen.

Intestines: In the adventitia of the smaller arteries there are also a number of nodules. All veins hyperemic.

Pancreas: n.a.d.

Suprarenal Glands: A group of smaller arteries show arterial changes of the vessels with marked fibrinoid necrosis and chronic inflammatory infiltration of the wall.

Thyroid: Venous hyperemia, otherwise n.a.d.


Tonsils: Chronic inflammatory changes. Epithelium and crypts infiltrated by inflammatory cells. In a few crypts there are cell debris and necrotic tissue. In the arteries there are similar changes to those described previously.

Lymph Glands: Chronic sinus catarrh, the vessels n.a.d.

Skin: n.a.d.

Prostate: Parenchyma n.a.d. A few small arteries show the same arterial changes as previously described.

Aorta: n.a.d. A small branch of an intercostal artery shows a nodular round cells infiltration in the adventitia with an area of necrosis.

Discussion

The difficulties presented by a diagnosis of polyarteritis nodosa during life can be explained by the variety of signs and symptoms of the condition. If one is justified in classifying the disease into various types, which is questionable, the reported case could be regarded as "cardiac type." The presenting symptoms were those of hypertensive congestive heart failure with transient pulmonary oedema. The clinical signs of pulsed alternans and gallop rhythm and the changing electrocardiograms were in favour with such a diagnosis while the persistent tachycardia and temperature and later the appearance of a rough systolic murmur were rather suggestive of a myocarditis. The apparent response to penicillin, shown by control of the temperature and the septic skin lesions, pointed to an infective cause. The high sedimentation rate was in full agreement with such a view. Even the abdominal pain would still have fitted in and could have been interpreted as evidence of multiple embolism in a case of endocarditis. Repeated negative blood cultures, however, the very moderate leucocytosis and the massive albuminuria in the absence of any appreciable haematuria were rather against a diagnosis of bacterial endocarditis. The acute onset of abdominal pain which is so often met in this condition may have been due to liver infarcts as revealed by the post-mortem findings. Pass (1935), in a review of the cases of hepatic infarcts in the literature, found polyarteritis nodosa to be the most frequent cause of such lesions. In fact Arkin (1930) has said that hepatic and renal infarcts in the absence of endocarditis should make one think of polyarteritis nodosa as the cause. The systolic murmur which developed eventually may have been caused by a relative mitral incompetence due to the rapid enlargement of the heart as there was no evidence of endocardial involvements at autopsy. The persistent tachycardia, out of proportion to the fever, the massive albuminuria, the lack of response to digitalis, the high sedimentation rate and the fact that the patient was obviously not aware of the severity of his condition were considered as characteristic features in the reported case.
SUMMARY

Some of the publications relating to polyarteritis nodosa are briefly reviewed and the pathology is discussed.

The original view that the condition carries an almost 100 per cent mortality has been modified and recent observers are quoted who state that more than 50 per cent of the patients recover. The possibility that the disease may run a prolonged intermittent course for many years is put forward. A few of the many theories regarding the etiology of the disease are mentioned. Of these the "allergic theory" is the more modern one.

The similarity of the histological changes in cases of polyarteritis nodosa and temporal arteritis suggests a common abnormality which may be a sensitizing antigen in both disorders. This would support the opinion of some observers that temporal arteritis is "an odd and relatively minor variant of periarteritis nodosa," White (1944), or a local manifestation of a more widespread disease.

Finally a case of polyarteritis nodosa, chiefly presenting cardiac symptoms, is recorded. Necropsy revealed the typical macroscopical and histological lesions in almost every organ, most marked in heart, liver, kidney and intestines.

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