GIANT-CELL OR TEMPORAL ARTERITIS: A REVIEW

BY

C. V. HARRISON

Postgraduate Medical School of London

Historical

The first case of what is now known as temporal, cranial, or giant-cell arteritis was published in 1890 by Jonathan Hutchinson. He described how the 80-year-old father of a London Hospital beadle came to him complaining that he could not put his hat on because of painful swellings in his temples. These proved to be red, inflamed, swollen temporal arteries which subsequently lost their pulsations and were left as hard cords after the condition healed. The man recovered and lived for a number of years. The next case was re-corded in 1930 by Schmidt. His patient showed the characteristic clinical picture and is of interest because he developed an intracranial aneurysm, a complication which has since been recorded in one other case (Andersen, 1947a). In 1932, Horton, Magath and Brown, of the Mayo Clinic, described two cases and, being presumably unaware of Hutchinson's and Schmidt's cases, regarded them as examples of a new disease and gave the condition the name of "temporal arteritis." They believed that the disease was limited to these arteries and followed a benign course free from complications. In 1934 and 1937 they recorded five further cases. In 1934 Paviot and others recorded the first case from France, but they did not mention any previously published cases and do not appear to have recognized the significance of their case. It is, however, interesting to note that their patient showed signs of involvement of the carotids as well as of the temporal arteries. In 1935 Barnard described the post mortem find-ings in a woman who had shown some of the signs of temporal arteritis and who had become blind. The temporal arteries were not described either in the clinical or autopsy account, but the description of the histology in the carotid and coronary arteries strongly suggests that this was an example of what is now called "giant-cell arteritis." In 1938 Jennings described the first two British cases corresponding to the descriptions of Horton and others, and he was the first to recognize blindness

as a complication of this disease. Since then cases have been recorded from U.S.A., Britain, France, and Scandinavia; the total of published cases to date is 75.

Nomenclature

This disease was first called "temporal arteritis" by Horton and others in the belief that it was localized in these arteries. As further cases were recorded it became apparent that this was far from true. Kilbourne and Wolff (1946), being impressed by the frequency of involvement of the cerebral and retinal vessels, suggested the term "cranial arteritis," and this was adopted by Curtis (1946) and Meyers and Lord (1948). A few writers have included the eponym "Horton's disease," but this has fortunately not been followed. Gilmour (1941) introduced the title "giant-cell arteritis" and this was followed by Robertson (1947).

None of these titles is satisfactory. The disease is far too widespread in its distribution for either "temporal" or "cranial" to be accurate, and giant cells have not been demonstrated in all cases. Nevertheless, on the score of simple accuracy, "giant-cell arteritis" is certainly the best title of the three. There is, however, one point in favour of retaining Horton's original term, and that is that it draws attention to the dominating and most diagnostic clinical lesion. It seems likely that the terms "temporal" and "giant-cell" will flourish side by side.

Clinical Characteristics

(For summary of findings in the reported cases see Table.)

Sex.—The early reports included a high propor-tion of women, but since then more cases have been reported in men, and the figures now are 35 men to 40 women, which suggests that there is probably no real sex bias.

Age.—Giant-cell arteritis is a disease of the elderly, the mean age of the 75 recorded cases being 65.3 years. The majority have been over 60,

o

and all but two over 50. The exceptions were women of 22 (Meyers and Lord, 1948) and 23 (Gilmour, 1941). Gilmour's case was clinically atypical, but the histology of the vessels appears to be characteristic; the case of Meyers and Lord was a typical one clinically, though the biopsy, taken during a recurrent attack, showed only a healed arterial lesion.

Onset.—The disease begins as a vague illness, with malaise, anorexia, bodily aches, sweats, and often fever. This prodromal stage may last from a few days (Bain, 1938 ; Dick and Freeman, 1940) up to eighteen months (Cooke and others, 1946; Andersen, 1947), but usually lasts about one or two months. At the end of this time the patient develops pain in the head. This is usually referred to the temple, and is severe, often enough to interfere with sleep. In many cases it is described as coming in attacks of great violence with a dull ache between the attacks. The pain usually resists ordinary analgesics and may not be fully controlled by morphia. Soon after the onset of pains in the head the temporal arteries become extremely tender; they usually appear as tortuous nodular cords covered by a red, inflamed skin. In the early stages pulsation is still palpable but this is usually lost during the height of the disease, though it may return later (Profant, 1944). Many of the clinical reports refer to the arteries as thrombosed; but thrombosis is unusual in the descriptions of the histology, and the hard, cordlike texture is probably due to a filling of the lumen by intimal proliferation rather than by clot. Enlarged cervical glands have been noted by MacDonald and Moser, 1937, Dick and Freeman, 1940, Hoyt and others, 1941, and Scott and Maxwell, 1941. The associated clinical findings are usually few. The patients are ill out of proportion to the physical signs; they may show mental changes (Sprague and MacKenzie, 1940 ; Schaefer and Sanders, 1942 ; Broch and Ytrehus, 1946), but examination of the central nervous system usually reveals no physical signs or only equivocal and transitory ones. The blood pressure in these patients is most often normal, and the number of cases with hypertension is probably no greater than would be expected in a control population of this age. Similarly the signs of generalized vascular sclerosis are no greater than is likely in a random group of elderly people.

Laboratory findings.—Almost every known laboratory examination has been performed on these patients, and particularly tests for bacterial agglutination. These, and also the Wassermann reaction, have been consistently negative. Blood examination alone has given any reasonably constant results. Anaemia of hypochromic type (60 to 85 per cent haemoglobin) has been recorded in twenty-nine cases ; it is rarely severe. A leucocyte count has been recorded in thirty-six cases and has varied from normal up to 24,500 per c.mm. of blood (Profant, 1944), the mean figure being 10,500 per c.mm. The blood sedimentation rate has been recorded as raised in twenty-one cases, and whilst the variety of methods used precludes any mean figure, the results recorded have mostly indicated a very abnormal figure. This raised sedimentation rate persists throughout the course of the clinical illness, and may continue for some time after symptomatic recovery. The cerebrospinal fluid has been examined in a number of cases and has sometimes shown a rise of protein and cells, but these findings appear to be inconsistent. Blood cultures have been consistently negative, as have electrocardiograms and radiographs.

Course.—The disease runs a slow course over many months. In the sixty-two cases in which the duration is stated, it has varied from about eight weeks to thirty months (Cooke and others, 1946). The mean for the stated figures is 7.2 months, but this is almost certainly an underestimate because in a significant number of cases the patient had not fully recovered at the end of the stated time. As a rule the severity of the symptoms diminishes and the patient is discharged from hospital without major symptoms but often still far from fit, and final recovery to normal health may be delayed for a number of months.

Prognosis.—In their early papers Horton and others stated that the disease ran a benign course free from mortality and complications. This has since proved to be incorrect. Of the seventy-five recorded cases, fifty-nine have recovered and sixteen have died ; but it is difficult to assess how many of these died as a result of the disease. This will be discussed later.

Treatment.—No effective form of therapy has yet been discovered. Individual cases have responded to the most diverse forms of treatment. The case of Paviot and others (1934) responded dramatically to salicylates, and those of Justin-Besançon and others, and of Lucien and others responded to sulphonamides; but many other cases have failed to respond either to sulphonamides or penicillin. The one form of therapy which has given the most constant symptomatic relief has been biopsy of the temporal artery. This had been recorded in twenty-one cases. In only two cases has it been specifically stated that biopsy failed to

afford relief (Sprague and MacKenzie, 1940; Dantes, 1946). The relief is symptomatic, does not seem to affect the course of the disease, and may be due to the coincidental cutting of perivascular nerves. Such nerves have been noted in the fibrosed adventitia by Lucien and others (1939) and by the present author.

Complications.—The commonest and most serious complication is involvement of the eyes. This had been noted in twenty-five out of seventy-five cases, and in fifteen of these there has been permanent blindness of one (eight cases) or both eyes (seven cases). In the majority of cases the ophthalmoscopic findings have been trivial compared with the loss of function, and it is generally believed that the blindness is due to retinal ischaemia from involvement of the vessels behind the globe and out of range of ophthalmoscopic examination. Johnson and others (1943) suggested that this may be due to vascular continuity between the temporal and ophthalmic arteries via the lachrymal branch of the former, but since we now know that the disease is, in fact, widespread and involves many vessels, it is unnecessary to postulate vascular continuity.

The second most important complication is cerebral involvement. The cases of Sprague and MacKenzie (1940), Schaefer and Sanders (1942), and Broch and Ytrehus (Case 3, 1946) showed clinical evidence of cerebral damage but recovered. The cases of Gilmour (Cases 2 and 3, 1941) and Cooke and others (Cases 3 and 6, 1946) died of cerebral ischaemia, confirmed at autopsy. The cases of Chasnoff and Vorzimer (1944), Cooke and others (Case 1, 1946), and Curtis (1946) died from cerebral causes but autopsy was not performed. In addition, the cases of Schmidt (1930) and Andersen (1947a) developed signs of intracranial aneurysm. From the records of the cases which came to autopsy there is little doubt that the cerebral signs and symptoms are due to involvement of the cranial vessels and are due to ischaemia. They may be transitory or they may be fatal, but generally they do not seem to leave any sequelae if the patient recovers; though there seems to be no reason why this should not occur. The two cases of Sjövall and Windblad (1944) both developed a crippling arthritis, but they are the only two recorded cases to do so and it is possible that they represent a coincidence rather than a complication. Robertson's (1947) first case developed gangrene of the leg, but again that may have been a coincidence due to atheroma. It is certainly significant that, in a disease which causes gross vascular narrowing and affects medium-sized arteries, there is no ischaemic gangrene of the limbs.

Fatal cases and the extent of the disease.—The cases which have died are of sufficient interest to justify individual consideration. The first was that of Barnard (1935). This woman had been ill for seven months with an apparently undiagnosed condition which was characterized by headache and the loss of sight in one eye. She died of erysipelas, and at routine autopsy changes were noted in the internal carotid and coronary arteries. These lesions were characterized by medial necrosis and cellular infiltration, including giant cells, and were interpreted as tuberculous though no bacilli were found. In the light of the numerous cases since recorded it seems highly probable that this was an example of giant-cell arteritis in which the involvement of the temporal vessels was minimal. A similar case has been recorded by Andersen (1947b).

Sproul and Hawthorne (1937) recorded two cases neither of whom showed any significant signs of temporal arteritis and both of whom died, one of septic kidney and the other of cardiac infarction. One case showed histological lesions in the aorta and iliac artery and the other in the aorta, iliac, and carotid arteries. The descriptions strongly suggest that in these cases the arterial lesion was indistinguishable from that of giant-cell arteritis, though the temporal arteries were not apparently involved clinically and were not examined at autopsy. The authors did not regard their cases as being examples of giant-cell arteritis, and Sproul does not refer to this publication in a later paper (1942), in which he records the autopsy findings in a classical case of giant-cell arteritis who died of ischaemic heart disease. In the latter case there were typical and severe lesions in the aorta, innominate, subclavian, pulmonary, coeliac, mesenteric, renal, and iliac arteries (the temporal arteries were not examined at autopsy though they were clinically typically affected during life).

Gilmour (1941) recorded four autopsy cases. The first was of a woman of only 23 who had been ill for six months with giddiness and hot sweats after an influenza-like onset and who died of a ruptured subclavian aneurysm. Clinically the case was atypical, but the histology of the aorta, internal, and external carotid and subclavian arteries was exactly similar to the published descriptions of classical cases and it seems probable that this was a true case. The age is quite unusual, but a clinically typical case has been reported in a woman of 22, by Meyers and Lord (1948). Gilmour's second case, in a woman of 59,

TABLE

RECORD OF PUBLISHED CASES OF GIANT-CELL ARTERITIS

No.	Authors	Case Nos.	Year	Sex	Age	Duration	Recovered or died	Biopsy	Autopsy	Eye symptoms or signs	Fever	Illness	B.S.R.	W.B.C.	Bodily pains	Anaemia	Relieved by biopsy	Vessels affected	Comments
1	Hutchinson		1890	M	80	?	R				+				?			Both temp.	Intracranial aneurysm
2	Schmidt		1930	M	69	8/12	R			Scotoma	+	+		3,900		+		Both temp.	
3	Horton et al.	1	1932	F	55	22/12	R	+			+	+		13,700				Both temp.	
4	"	2	1932	M	68	2/12	R	+			+	+		10,600	+		+	Both temp.	Associated with active rheumatism.
5	Paviot et al.		1934	M	61	3/12	R			Unequal pupils		+				+		Both temp., both carotid.	
6	Barnard		1935	F	63	7/12	D		+	L. blind	+	+		8,600				Carotid and coron.	Glands +. Root abscess.
7	MacDonald and Moser	1	1937	F	60	6/12	R	+			+	+						Both temp.	
8	Horton and Magath	2	1937	F	69		R				+	+						Both temp.	
9	"	3	1937	F	75		R	+			+	+						Both temp.	
10	" "		1937	M	72		R					+						Both temp.	
11	" "		1937	F	65	6/12	R	+			+	+						Both temp.	
12	" "		1937	F	68	2/12	R	+				+						Both temp.	
13	" "		1937	M	57		D			L. blind								Both temp.	Died of septic kidney.
14	Sprout and Hawthorne	1	1937	M	76		D		++									Aorta and iliac.	Died of cardiac infarct.
15	"	2	1937	M	50		D		++									Aorta, iliac, carotid.	
16	Jennings	1	1938	F	66	6/12	R	+		L. blind	+	+	+	13,000	+	++		Both temp.	
17	"	2	1938	F	72	10/52	R				+	+		9,100		++		Both temp.	
18	Bain		1938	F	71	9/12+	R	+			+	+		12,500				Both temp.	
19	Thévenard		1939	M	66		R				+	+						Both temp. and occipital.	
20	Lucien et al.		1939	F	79		R	+			+	+		3,500	+		+	Both temp. and occipital.	Glands +. Followed pneumonia.
21	Dick and Freeman	1	1940	F	65	3/12	R	+		L. reduced field	+	+		13,100			+	Temp., pariet., and P. auric.	Glands +. inflamed. Tonsils
22	"	2	1940	F	76	13/12	R			Blurred vision	+	+	N		+			Both temp.	Became mentally sluggish.
23	Bowers	1	1940	F	65	6/12	R	+			+	+	++			+++	+	Temp. and occipital	
24	Sprague and MacKenzie		1940	M	66	6/12+	R	+				+	++	12,900	+	+++	—	Both temp.	Glands +. Inflamed fauces.
25	Hines		1941	F	69	6/12	R	+				+	+	20,000	+++		+	R. temp. and radial.	Glands +.
26	Hoyt et al.	1	1941	F	58	7/52+	R	+			+	+		14,000			+	Both temp.	Glands +.
27	"	2	1941	F	61	7/52	R	++			+	++		10,300	+++	+	+	Both temp.	
28	"	3	1941	F	67	3/12+	R	++			+							Temp., facial, and carotid.	
29	Scott and Maxwell		1941	F	70	6/12+	R			L. blind		+							
30	Gilmour	1	1941	F	23	6/12	D		+			+						Aorta, carotid, and subcl.	Died of ruptured subclavian aneurysm. Cerebral infarct.
31	"	2	1941	F	59	5/12	D		+		?	+			+	+		Aorta, carotid, cerebral.	Cerebral infarct.
32	"	3	1941	M	63	9/12	D		++	Failing vision		++	+	4,000	—	+		Aorta and carotid.	Cerebral infarct. Post-operative death. Healed arteritis.
33	"	4	1941	F	64	26/12	D											Aorta, innom., subcl., carotid, and iliac.	
34	Sproul		1942	M	68	8/52	D		+			+	+	17,000				Temp. and others.	Many major vessels affected.
35	Plaut		1942	F	63	10/52	R			Ptosis		+++			+++			Both temp.	
36	Schaefer and Sanders		1942	F	62	3/12	R	+		L. blind	+	+++		9,700	+		+	R. temp.	
37	Oldberg		1942	M	64	6/12	R					+						Both temp.	
38	Murphy		1942	F	71	6/12	R	++										Both temp.	
39	Johnson et al.	1	1943	F	61	3/52+	R	++		Both blind		+						Both temp.	
40	" " "	2	1943	M	75		R			One blind								Both temp.	
41	" " "	3	1943	F	80		R			R. blind								Temp.	
42	" " "	4	1943	F	76	4/12+	R					+	+			+		Both temp.	Delirious. C.S.F. changes

TABLE—continued.

No.	Authors	Case Nos.	Year	Sex	Age	Duration	Recovered or died	Biopsy	Autopsy	Eye symptoms or signs	Fever	Illness	B.S.R.	W.B.C.	Bodily pains	Anaemia	Vessels affected	Relieved by biopsy	Comments
43	Brown and Hampson		1944	M	61	6/12+	R	+	+	—	—	+		9,200	+		Temp. and occipital.	+	Died in coma 3/12 after biopsy. P.M. details not published.
44	Chasnoff and Vorzimer		1944	F	63	14/12	D	+	+	—	+	+	+		+	+	Temp. and internal.	+	Flare up after tooth extn. Pulsations reappeared.
45	Profant	1	1944	F	76	12/12	R	—	—	—	++++	++++		24,500	—	—	R. temp.		
46	„	2	1944	F	61	2/12+	R	+++	—	—	++++	++++	++	12,000	+	++	Both temp.	+	
47	Sjövall and Windblad	1	1944	M	62	12/12	R		—	—	+	+		5,900			Both temp.	+	Developed arthritis.
48	„	2	1944	M	63	9/12	R	+	—	—	+	++		7,300			Both temp.	+	Developed arthritis.
49	Shannon and Solomon		1945	M	73	12/52	R	+	—	Both blind							Temp. and ? occipital.	+	
50	Cooke et al.	1	1946	M	66	5/12	D	+	—	L. blind	+	+		11,800	+		Temp. and ? limb.	+	Died cerebral death 6/52 after discharge. No P.M.
51	„	2	1946	F	66	6/12+	R		—	Both blind	+	++		10,700	++	++	Both temp.		
52	„	3	1946	F	69	30/12	D	+	+	Both blind				5,100			Both temp., aorta, and femoral.		Died of cerebral damage.
53	„	4	1946	M	71	6/12+	R	++	—	Vision impaired	+	+		8,400	+	+	Both temp.	++	Had second attack. ? limb arteries involved.
54	„	5	1946	M	69	12/12	R	+	—	—		+		10,000	+		Temp. and occipital.	+	
55	„	6	1946	F	73	14/12	D	+	+	Both blind	+	+		8,300	+	+	Temp. and radial, and others.	+	Cerebral death. Many int. arteries affected.
56	„	7	1946	F	68	12/12+	R	+	—	—	+	+		13,200	+	+	Temp. and occipital.	+	
57	Broch and Ytrehus	1	1946	M	69	5/12	D	—	—	Squint	+	—	+			+	Both temp.		Died 2/12 later of haematemesis. No P.M.
58	„	2	1946	M	76	12/12	R		—	—		+	+++		+	+++	Both temp.		Mental changes.
59	„	3	1946	F	67	6/12	R		—	—					+|		Both temp.		
60	„	4	1946	M	74	12/12	R	+++++	—	—							Both temp.		
61	Curtis		1946	F	71	4/12+	D		—	Both blind					+		Temp. and leg.		Cerebral death. No P.M.
62	Dantes		1946	M	55	6/12+	R		—	—					+|	+|	Temp. and limb.		Dorsalis pedis involved.
63	Gordon and Thurber		1946	M	65	19/52	R		—	Retinal exudate							Both temp.		
64	Kilbourne and Wolff		1946	M	68	3/12	D		—	—		+		13,600	+	+	Both temp.		Died of cardiac infarct 3/12 later. No P.M.
65	Andersen		1947a	M	54	24/12	R	+	—	Glaucoma	+	+	+	7,300	+	+	Both temp.	+	Left with limb pains and intracranial aneurysm.
66	Andersen		1947b	F	63	5/12	R	+	—	—	+	+	+	4,700	+	+	Temp. and leg.	+	
67	Robertson	1	1947	M	65	12/12	R	+	—	—	+	+	+	6,600	+	+	Temp., facial, occip. and leg.	+	Temp. arteries less affected than others.
68	„	2	1947	M	65	2/12+	R		—	Both blind	+	+	+	9,000	+	+	Temp., facial, and occip.	+	Leg gangrene, ? cause.
69	„	3	1947	F	73	?	R		+	—					+		Temp., facial, and occip.		
70	„	4	1947	M	67	?	D		—	—							Temp. and occipital.		Died P.G.U. No P.M. histology. Thrombus in subclavian.
71	Justin-Besançon et al.		1948	F	70	4/12	R	+	—	—	+	+		10,500	+	+	Temp., occip. and facial.	+	? similar attack 3 years before.
72	Meyers and Lord		1948	F	22	3/12	R.	+	—	—	+	+					L. temp.	+	Biopsy in recurrent attack, healing lesion.
73	Cohen and Harrison	1	1948	M	72	15/52	R	++	—	—	|+	+		12,800	+	+	Both temp.	++	
74	„	2	1948	M	65	8/52	D		—	—							Both temp.		Died 6/12 later from cardiac infarct. No P.M.
75	„	3	1948	M	69	23/52	R	+	—	L. blind	|.		+	6,200		—	Both temp.	+	

had a five months' illness starting like influenza and characterized by temporal pain and noises in the head. She died in coma and at autopsy showed thrombosis of the internal carotid artery, and giant-cell arteritis of it and of the aorta. Gilmour's third case, a man of 63, had a nine months' illness with headache, mental signs, and failing vision. He too died in coma and at autopsy showed thrombosis of the internal carotid arteries and giant-cell arteritis of the aorta and of the external and internal carotid arteries. In Gilmour's fourth case, a woman of 64 suffered an ill-defined disease for twenty-six months and never showed any indication of temporal arteritis. She died of enteritis and amyloid kidneys, but at autopsy the aorta, innominate, common carotid, subclavian, and iliac arteries showed what the author interpreted as the healing stage of giant-cell arteritis. Chasnoff and Vorzimer (1944) record a case with typical histological appearances in the biopsy specimen of the temporal artery. Three months after discharge the patient returned to hospital in coma and died. The authors stated that at autopsy other internal arteries were involved and that details were to be published later by Mahoney and Hall, but no such publication can be traced.

Cooke and others (1946), in a series of seven typical cases of temporal arteritis, record three that died. Their first patient died from cerebral causes six months after discharge, and no autopsy was performed. Their second died from cerebral causes, and giant-cell arteritis was found in the aorta and in the femoral and mesenteric arteries. Their third also died from cerebral causes, and giant-cell arteritis was found in the aorta and in the superior mesenteric, femoral, radial, and retinal arteries. Broch and Ytrehus (quoted by Andersen, 1947a) record a typical case in which the patient died of haematemesis two months after discharge from hospital, but no autopsy was performed. Curtis (1946) described a patient with typical histological appearances in the biopsy specimen of the temporal artery who was readmitted in coma eighteen days after discharge and died, but no autopsy was carried out. Kilbourne and Wolff (1946) report a patient with typical biopsy findings who died of cardiac infarction three months later ; no autopsy was carried out. Robertson (1947) recorded a clinically typical patient who died a month later of a perforated gastric ulcer. At autopsy the subclavian artery was thrombosed but, unfortunately, no sections were taken.

The inclusion of some of these sixteen cases is open to criticism on the ground that as they did not show the clinical signs of temporal arteritis

during life, therefore the arterial disease found at autopsy is something different. Dantes (1946) has denied the authenticity of the cases of Barnard, Gilmour, and Sproul and Hawthorne. In the author's opinion this criticism is not justified for the following reasons. There is undeniable clinical and autopsy evidence that temporal arteritis is a widespread vascular disease. The clinical syndrome on which the diagnosis depends is the result of involvement of the superficial temporal arteries, and if these are excised for biopsy one of the dominant symptoms (localized head pain) usually disappears. If, therefore, a case of "temporal arteritis" should occur in which the temporal arteries were not involved the only really diagnostic clinical features would be lacking. In the cases recorded by Cooke and others, Sproul, and Chasnoff and Vorzimer the diagnosis was established clinically and was beyond question, and in these the larger internal arteries were involved. In the cases of Barnard, Gilmour, and Sproul and Hawthorne, the internal arteries showed apparently similar lesions, but the temporal arteries were not noted clinically or examined histologically and are, therefore, presumed not to have been involved. Nevertheless, it seems reasonable to assume that these were true cases and that in them the temporal arteries were either not involved or involved so slightly that they were overlooked.

These sixteen cases may give an exaggerated impression of the fatality rate in temporal arteritis. The cases of Barnard, Sproul and Hawthorne, and Gilmour (Case 4) did not die of their arterial disease. The cases of Sproul, Chasnoff and Vorzimer, Broch and Ytrehus, Curtis, Kilbourne and Wolff, and Robertson may have died of other diseases and not directly of the arteritis. Nevertheless, in the light of the first three cases of Gilmour and the second and third cases of Cooke and others, there is no doubt that temporal arteritis can prove fatal by cerebral involvement and it seems likely that it may also be fatal by involving other vital arteries.

These autopsy cases also illustrate the widespread nature of the disease, a point which has been stressed by clinical observers. Giant-cell arteritis is a disease of the larger arteries. The characteristic lesions have been described microscopically in the aorta nine times, in the carotid arteries six times, in the iliac arteries four times, in the mesenteric and subclavian arteries three times, in the innominate and femoral arteries twice, and in the pulmonary, coronary, coeliac, renal, radial, and retinal arteries once each. Most of these are arteries which are readily accessible dur-

ing the course of a routine autopsy, and the implication is that the disease is likely to affect any of the elastic and larger muscular arteries. It seems highly probable that other, less accessible, arteries were affected in these cases but were not examined.

Another point which emerges from these autopsy reports is the irregular distribution of the lesions. In most cases a number of vessels other than those listed above were examined and found unaffected. A further point is that the disease is apparently limited to arteries; the only reference to veins is made by Cooke and others, who state that the femoral vein was involved in one of their autopsy cases. It is, of course, possible that minor grades of venous involvement might be found if veins were systematically examined, but it is unlikely that the disease affects them severely or the naked-eye changes would have been noted. Apart from the larger arteries noted at autopsy there is clinical evidence that other arteries than the temporal are involved, especially the palpable vessels of the head. The vessels noted clinically are as follows: occipital artery (Lucien and others; Bowers; Brown and Hampson; Shannon and Solomon; Cooke and others; Robertson; Justin-Besançon and others); facial artery (Scott and Maxwell; Robertson; Justin-Besançon and others); carotid artery (Paviot and others; Scott and Maxwell); parietal artery (Dick and Freeman); posterior auricular artery (Dick and Freeman); radial artery (Hines); dorsalis pedis (Dantes).

Pathology

The lesions in the temporal arteries.—The following account of the morphology of the lesions is based partly on the published reports and partly on a personal examination of five cases. The gross morbid anatomy is not characteristic. The vessels are bigger than normal and may be nodular. They appear to be solid cords with little or no lumen. Histologically the lesions are much more striking and characteristic (Plate Ia) but vary a good deal in their distribution. At different levels within one short segment of artery the lesion may vary in its intensity, in the presence or absence of the characteristic giant cells, and in the proportion of the circumference involved. In a suspected case, if the histology is atypical it is wise to cut deeper into the block. The lumen is usually reduced to a minute hole or slit and may be thrombosed, but thrombosis is the exception rather than the rule. It has been stated to be present thirteen times and absent thirty times, and probably represents no more than an incidental complication. It is certainly true that thrombosis plays no essential

part in the development of the lesion—a significant point of differentiation from Bürger's disease. The intima shows gross thickening, thus accounting for the diminished lumen. This is invariably present and has been mentioned in every histological report. The intimal thickening may be either concentric or eccentric, usually depending on whether the whole circumference of the media or only a part of it is affected.

During the active stage of the disease this intimal proliferation is often divisible into two different zones (Plate V). The inner one, which is usually the thicker, consists of a cellular fibrous tissue of loose texture with relatively few inflammatory cells or vessels. In the interstices between the fibroblasts there is a pale-staining background which has been described by Sjövall and Windblad (1944) and Gordon and Thurber (1946) as oedema, and by Brown and Hampson (1944), and by Gilmour (1941) as mucoid. In the cases which I have examined this material has been of mucoid nature (Plate IVa) and apparently identical with the mucoid interstitial tissue described by Schultz (1922) and Ssolowjew (1924) in all arteries, and so constantly seen in excess in medionecrosis of the aorta. It seems probable that it represents a normal product of the connective-tissue cells of arteries.

In the outer part of the intima the picture is usually one of a much more active inflammatory response, but this is not always so; some arteries lack this zone entirely (Plate IIb). There are often young capillaries (Plate V) and nearly always an inflammatory cellular infiltration. The cell response varies from one case to another. Lymphocytes, macrophages, plasma cells, and polymorphonuclears may be present in variable proportions, and some giant cells may be seen. Eosinophils are rarely present and are practically never a marked feature—a point of distinction from polyarteritis nodosa. The media usually shows the maximum damage and is often virtually destroyed. Frank coagulative necrosis is frequently present (Plate V) and has been specifically mentioned in twenty-one reports. Cellular infiltration is always present and is rather variable. Lymphocytes and macrophages always appear to be present (Plate IIb and III), and there are usually some polymorphonuclears but they are rarely the dominant cell. Eosinophils are occasionally mentioned (Bowers; Hoyt and others; Kilbourne and Wolff) but never as a dominant cell.

The characteristic giant cells (Plate IIb and III) are mentioned as present in thirty-eight cases and can be inferred to have been present in most of the others. They were apparently not present in the

cases of Kilbourne and Wolff, Gilmour (Case 4), and Sjövall and Windblad (Case 2). I have seen a case in which no giant cell was present in the first few sections of a biopsy specimen but plenty were present deeper in the block, and it seems probable that all or nearly all cases will show giant cells if the specimen is cut at different levels. These giant cells are of foreign-body type and of irregular shape, sometimes rounded, sometimes elongated. They vary in size from cells of 10μ with two or three nuclei, up to masses of 100μ with very many nuclei. The latter may be distributed in any way, usually being quite haphazard, but sometimes arranged round the periphery exactly like the giant cells of a tubercle. The nuclei resemble those of the neighbouring macrophages, and the cytoplasm has an eosinophilic ground-glass appearance. Some of these giant cells lie in relation to fragments of elastic tissue (Plate IVb) and presumably represent an attempt at its removal, but others occur in the thickened intima in situations away from demonstrable elastica. The internal elastic lamina usually shows severe destruction (Plate IIb). This is recorded in twenty-eight cases and can be inferred from some of the other reports. It is generally fragmented into short lengths, and these may disappear. Sometimes the fragments assume odd shapes. In some cases there is a later overgrowth of new elastica (Cooke and others). These medial lesions are generally rather diffuse, involving large segments or the whole circumference, but in some cases they occur in a curiously focal form. This was so in Barnard's case, where they resembled tubercles, and is beautifully depicted in Fig. 4 of the paper by Cooke and others (1946).

The adventitia is involved to a variable extent (Plate IIa). The adventitial lesions were stressed by Horton and others in their original papers, but subsequent observers appear to have been more impressed by the medial changes. Cooke and others suggest that the lesion spreads along the vessels by the vasa vasorum in the adventitia. In the majority of cases there is a cellular infiltration of the adventitia, contiguous with and similar to that of the media but lacking giant cells. This is usually associated with an overgrowth of adventitia fibrous tissue. The vasa vasorum may be cuffed by inflammatory cells; this has been stressed by Gordon and Thurber and by Kilbourne and Wolff. In some cases nerves are visible embedded in the fibrosed adventitia (Lucien and others, 1939; Cohen and Harrison, 1948). Such involvement of nerves may account for the pain in the temporal regions and for its relief when a biopsy is performed.

Giant-cell arteritis in larger arteries.—In the cases which have come to autopsy the morphology of the lesions in the larger arteries has been essentially similar to that in the temporal arteries. Furthermore, the descriptions in the clinically uncertain cases of Barnard, Gilmour, and Sproul and Hawthorne tally exactly with those of the clinically proved cases of Cooke and others and of Sproul.

Macroscopically the vessels (aorta, carotid, etc.) may not show any obvious lesion or they may show a smear of fibrin clot overlying the lesion. Microscopically the damage affects mainly the media. The intima may show some recent fibroblastic proliferation, but this is slight and may be absent. Cellular infiltration of the intima is the exception rather than the rule. In the media the striking lesion is a cellular infiltration in which lymphocytes and plasma cells dominate, though a few polymorphonuclears may be seen. Giant cells are always present (Gilmour's Case 4 is an exception) and are of the same type as those in the temporal arteries. They may be found in association with fragments of elastica. Necrosis is usually only a cellular one, with disappearance of muscle in the affected areas, but occasionally foci of dead tissue may be seen. Some destruction of elastica is nearly always present, but it is slight and affects only few fibres. There may be increased vascularity of the media, but this is not striking. In the adventitia, changes are slight or absent. There may be some fibrosis, and there may be some cellular infiltration similar to that of the media.

In arteries intermediate between the common carotid and the temporal the lesions are also intermediate, and there is a greater tendency to thickening of the intima and to thrombosis.

From a study of these cases there seems to be no reasonable doubt that the giant-cell arteritis observed in the larger arteries is the same as that in the temporal arteries and that the disease is widespread.

Aetiology

Nothing is known of the aetiology of giant-cell arteritis. There are, however, certain points which appear significant. It affects white races only; at least no cases have been recorded in coloured races. The early cases (Horton and others) were mostly in farmers and country dwellers, but this has not been the rule in subsequent cases. On the whole, middle-class and well-to-do patients seem to have been rather more frequently affected, but no occupation has been unduly represented. There is no evidence of a familial incidence. No organisms have been recovered with any regularity from
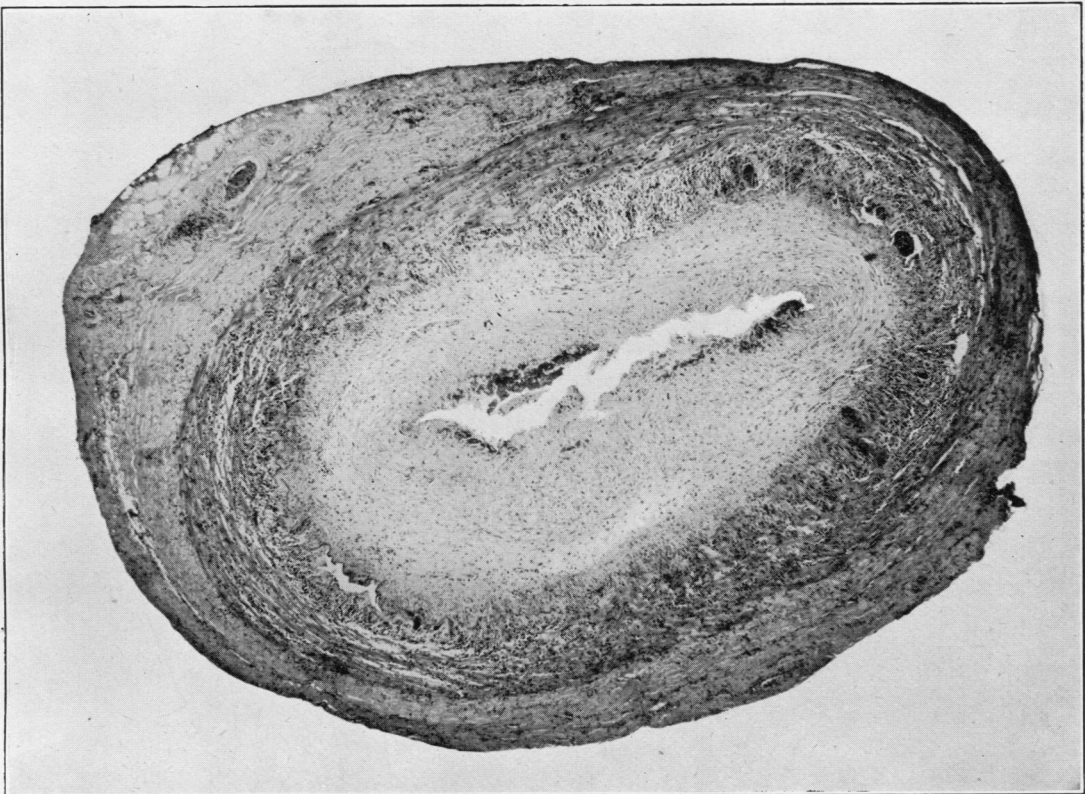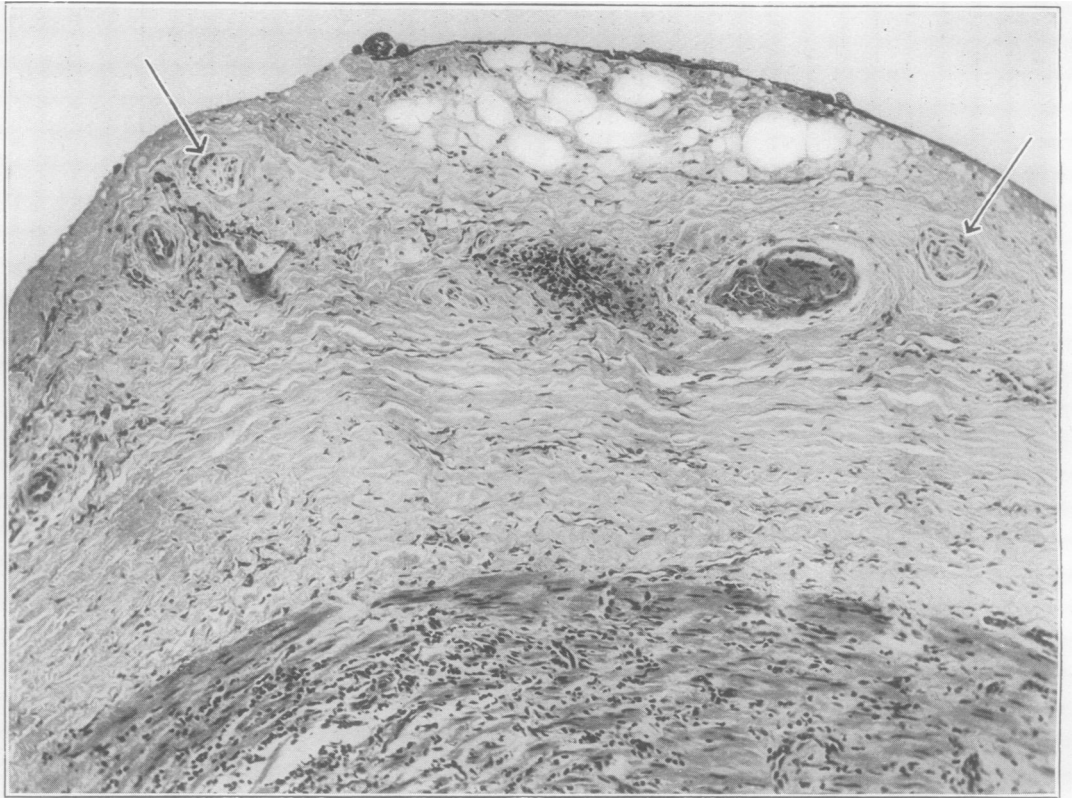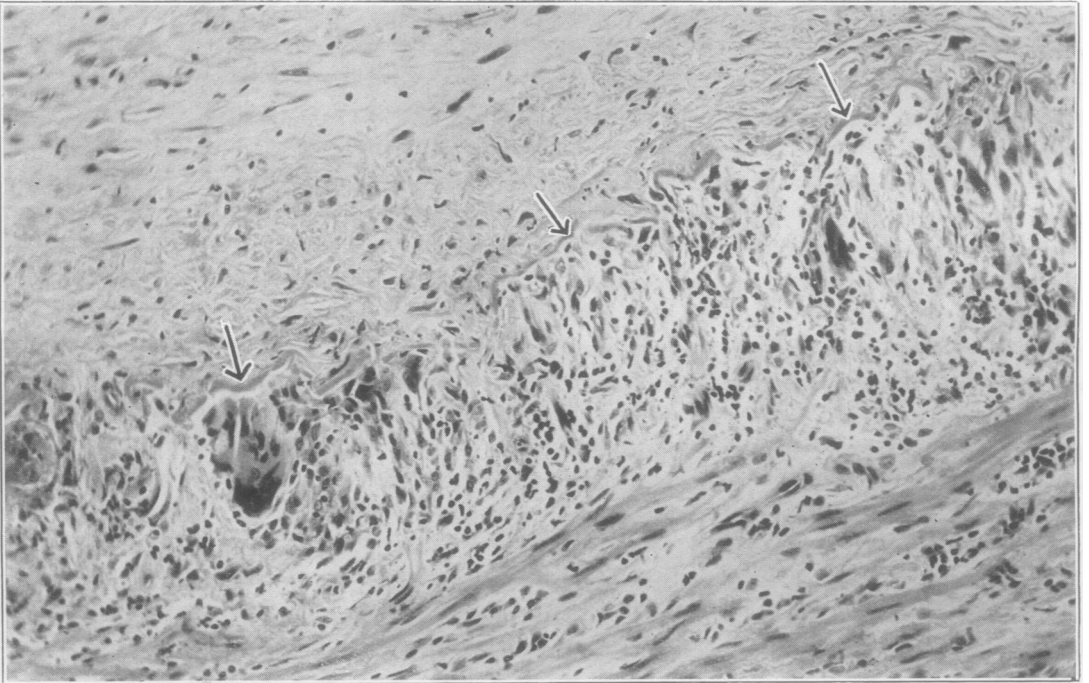
(a)

(b)

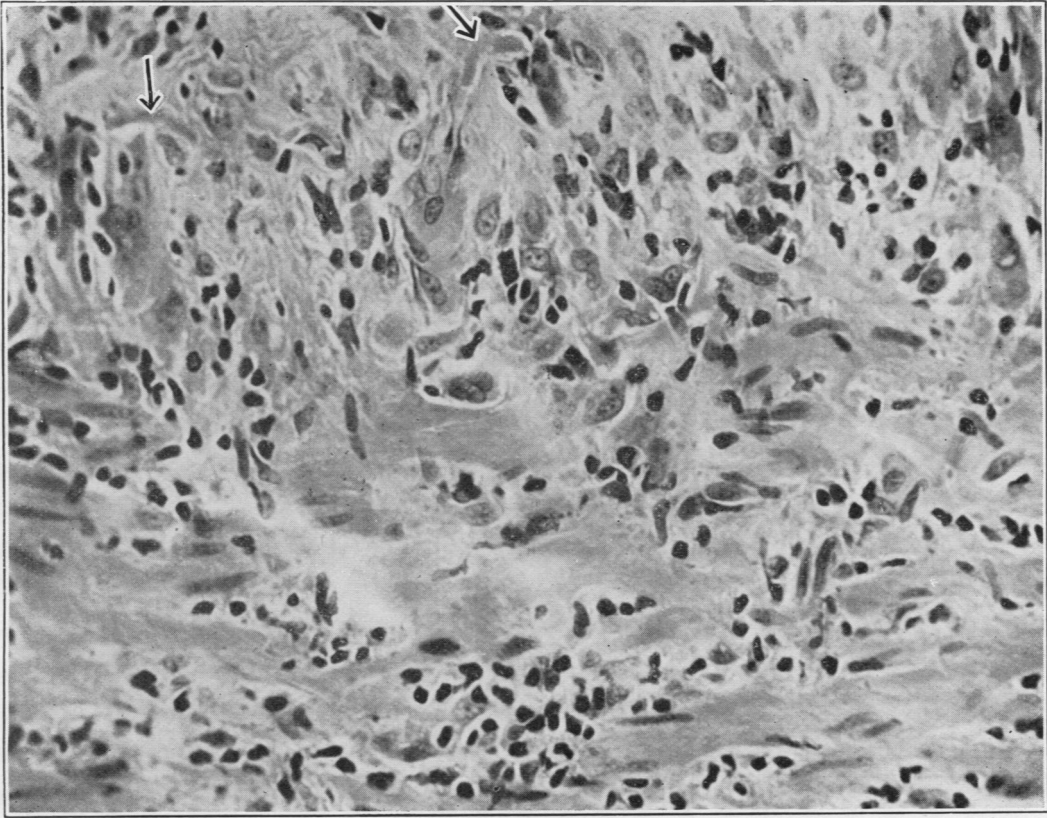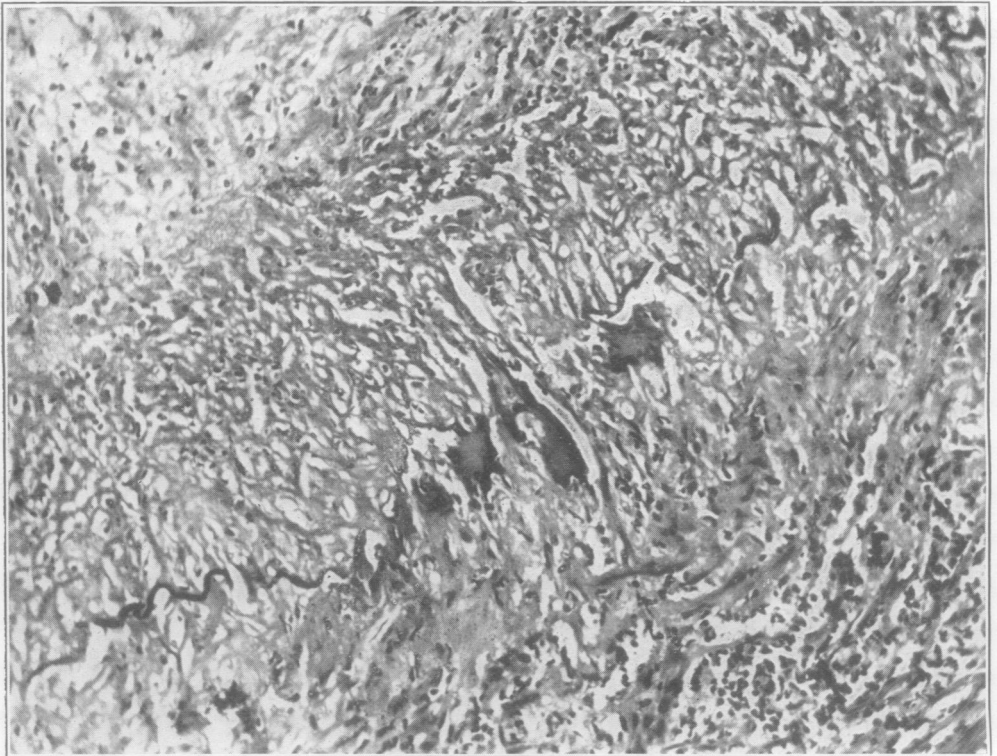PLATE I.

(a)

(b)

PLATE II.

PLATE III.

PLATE I.—(a). Section of temporal artery. There is a little mural thrombus adhering to the intima which is greatly thickened. The media is still visible but heavily infiltrated, and it contains many giant cells. The adventitia is fibrosed. (Haematoxylin and eosin, × 40.) (b). Same case as (a). Showing the fragmentation of the internal elastic lamina and the formation of new elastic fibres in the deeper part of the intima. (Weigert's elastic and neutral red, × 80.)

PLATE II.—(a). Same case as Plate I. Showing adventitia and outer part of media. The adventitia is fibrosed and shows a little cellular infiltration. Note two small nerves embedded in fibrous tissue. (Haematoxylin and eosin, × 120.) (b). Same case as Plate I. The intima (upper left) consists of cellular fibrous tissue. The internal elastic lamina (arrows) is fragmented. The media is heavily infiltrated with inflammatory cells and there are numerous giant cells near the elastic lamina. Note that the innermost layer of the media is more severely affected than the rest. (Haematoxylin and eosin, × 190.)

PLATE III.—Same case as Plates I and II. Innermost layer of media showing infiltration with lymphocytes and macrophages and the formation of giant cells, apparently from macrophages. The arrows indicate fragments of the internal elastic lamina. (Haematoxylin and eosin, × 430.)
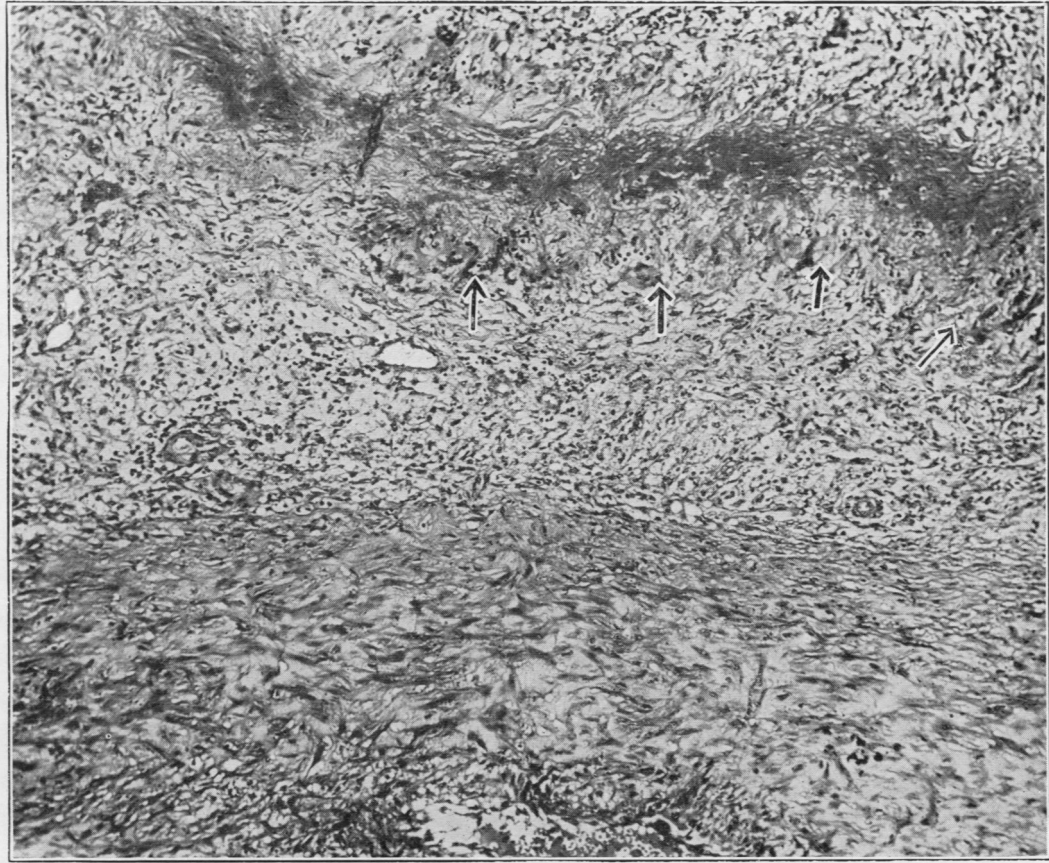
(a)

(b)

PLATE IV.

PLATE V.

PLATE IV.—(a). Temporal artery. Second case. Innermost layer of thickened intima showing proliferating fibroblasts lying in a background of mucoid connective tissue. (Haematoxylin and eosin, × 460.)
(b). Same case as (a). Junction of intima and media showing giant cells lying against fragments of the internal elastic lamina on its medial side. Note the cellular infiltration of both media and intima. (Verhoeff and Van Gieson, × 190.)

PLATE V.—Temporal artery. Third case. The lumen is just visible at the bottom of the section. The inner part of the intima consists of active mucoid fibroblastic connective tissue. The outer part of the intima consists of vascular granulation tissue. The remnants of the internal elastic lamina are shown by arrows. The media shows a band of necrosis. (Haematoxylin and eosin, × 120.)

excised arteries. Horton and others grew a type of actinomyces from one of their early cases but decided that this was a contaminant, and certainly no one has since grown a similar organism. MacDonald and Moser grew a staphylococcus which they regarded as a contaminant. Other workers (Andersen; Lucien and others; Scott and Maxwell) have failed to grow any organisms from excised arteries. All attempts to grow organisms from blood culture have been unsuccessful (Andersen; Chasnoff and Vorzimer; Schaefer and Sanders). Finally, many workers have searched for organisms in stained sections, all without success. Yet in spite of these completely negative results, there is indirect evidence which suggests that the disease may have an infective basis; it certainly seems to have an association with infection. Gilmour's four cases all began with an influenza-like onset, and Schmidt's dated from an attack of influenza. Dick and Freeman's first case followed an attack of pneumonia, and Paviot and others' case followed the extraction of a septic molar. MacDonald and Moser's case had a dental-root abscess, and Brown and Hampson's was associated with dental sepsis. Dick and Freeman's second case and Hoyt and others' case had faucial sepsis. All these may have been coincidental, but the fact that one of Horton and others' cases recovered after the extraction of septic teeth, and that Profant's case showed a clinical flare-up after the extraction of a septic tooth, strongly suggests that the arteritis and the sepsis were related. Paviot and others' case had further interest in that this subject also had active rheumatic carditis at the time, and both this and the arteritis responded dramatically to salicylates—a form of therapy which no one else records having tried except for the use of aspirin as an analgesic. Lastly, both of Sjövall and Windblad's cases developed crippling arthritis, whilst Andersen's was left with " rheumatoid pain " in his lower limb.

Apart from its apparent associations with infection there are features in the disease itself which suggest infection. The fever, the leucocytosis, the enlarged cervical glands, and the high sedimentation rate, together with the general illness of the patient, all suggest some sort of infective process. Naturally, the failure to find any organism in a disease of an apparently infective type suggests an allergic response, but Dantes (1946) rejects this hypothesis on account of the lack of eosinophils in the lesions and of other signs of allergy in the patients. So far apparently no attempt has been made to isolate a virus. Thus, at present the data available suggest that giant-cell arteritis is possibly of infective origin, but there is no clue as to the type of infection or the mode whereby infection produces the changes.

Comparison with Other Diseases

A number of workers (Jennings; Gordon and Thurber; Kilbourne and Wolff; Hoyt and others; Andersen) have compared giant-cell arteritis with other arterial diseases, particularly thrombo-angiitis obliterans and polyarteritis nodosa. Only with the latter does it bear any close comparison, and the question arises whether giant-cell arteritis has sufficient characteristics of its own to justify regarding it as a separate entity and, if so, how closely it is allied to polyarteritis nodosa. If one analyses the clinical picture and the morphology of the arteries, as some workers have done, then there are many points in common and no feature which is absolutely characteristic of either disease. Nevertheless if giant-cell arteritis—either as a clinical entity or as a histological picture—is viewed as a whole, then there is no question of its not being a real recognizable entity.

The clinical differences between giant-cell arteritis and polyarteritis nodosa depend on two basic factors: age, and the arterial territory involved. Polyarteritis is a disease of young adults and affects the small muscular arteries in the viscera: giant-cell arteritis is a disease of the elderly and affects the elastic and larger muscular arteries proximal to the point where they break up to enter the viscera. The histological differences depend largely on the acuteness of the process. Polyarteritis is often acute, whilst giant-cell arteritis is subacute. The signs of an active infection—the fever, illness, leucocytosis, anaemia, etc. —are common to both. The clinical pictures depend for their differentiation on the territory involved. The differentiating signs of giant-cell arteritis—the headache, palpable temporal arteries, eye involvement, and nervous signs—depend on the involvement of the larger cranial vessels. Similarly the signs of polyarteritis—the renal lesions, cardiac signs, abdominal signs—are the result of visceral ischaemia from involvement of small visceral arteries.

In a similar way the histology of giant-cell arteritis (the lymphocytes and plasma cells, the giant-cells, the fibroblastic reaction) are all those of a subacute disease, whilst the histology of polyarteritis nodosa (the polymorphonuclears and eosinophils, the fibrinoid necrosis, the aneurysms) are all those of an acute process.

There is one final point of difference: polyarteritis is probably an allergic response (Rich and Gregory, 1943; McKeown, 1947); whilst there is no

evidence, either clinical, morphological, or experimental, to suggest that giant-cell arteritis is of this character.

Summary

1. Giant-cell arteritis is a disease of the elderly of either sex.

2. It runs a course of about six months and is characterized by malaise, fever, severe headaches and prominent, thick, painful temporal arteries; it is usually accompanied by leucocytosis, anaemia, and raised sedimentation rate.

3. There is no specific treatment, but the disease tends to subside slowly and complete recovery is the rule.

4. It may be complicated by blindness or cerebral disturbances from involvement of appropriate arteries.

5. In some cases the disease has proved fatal, and it has been shown to involve many arteries of the elastic and large muscular group, from the aorta down.

6. In most cases a number of cranial arteries are involved.

7. The arterial lesions are characterized by lymphocyte and plasma-cell infiltration of the media with frequent giant cells. The elastica is usually broken up, and the intima undergoes fibroblastic proliferation. There is usually some fibrosis and cellular infiltration of the adventitia. The disease appears to be infective but its aetiology is unknown.

8. The relationship of the disease to polyarteritis nodosa is discussed.

My thanks are due to Mr. E. V. Wilmott, A.R.P.S., who prepared all the photomicrographs.

REFERENCES

Andersen, T. (1947a). *Acta med. scand.*, **128**, 151.
Andersen, T. (1947b). *Acta med. scand.*, **128**, 230.
Bain, C. W. C. (1938). *Lancet*, **234**, 517.
Barnard, W. G. (1935). *J. Path. Bact.*, **40**, 433.
Bowers, J. M. (1940). *Arch. intern. Med.*, **66**, 384.
Broch, O. J., and Ytrehus, O. (1946). *Nord. Med.*, **30**, 1251. (Quoted by Andersen.)
Brown, J. W., and Hampson, F. (1944). *Brit. Heart J.*, **6**, 154.
Chasnoff, J., and Vorzimer, J. J. (1944). *Ann. intern. Med.*, **20**, 327.
Cohen, H., and Harrison, C. V. (1948). *J. clin. Path.*, **1**, 212.
Cooke, W. T., Cloake, P. C. P., Govan, A. D. T., and Colbeck, J. C. (1946). *Quart. J. Med.*, n.s., **15**, 47.
Curtis, H. C. (1946). *Amer. J. Med.*, **1**, 437.
Dantes, D. A. (1946). *J. Amer. med. Ass.*, **131**, 1265.
Dick, G. F., and Freeman, G. (1940). *J. Amer. med. Ass.*, **114**, 645.
Gilmour, J. R. (1941). *J. Path. Bact.*, **53**, 263.
Gordon, L. Z., and Thurber, D. C. (1946). *Arch. Path.*, **42**, 402.
Hines, E. A. (1941). In "Diagnosis and Treatment of Cardiovascular Disease," edited by W. D. Stroud. Second Edit., p. 1681.
Horton, B. T., Magath, T. B., and Brown, G. E. (1934). *Arch. intern. Med.*, **53**, 400.
Horton, B. T., and Magath, T. B. (1937). *Proc. Mayo Clin.*, **12**, 548.
Hoyt, L. H., Perera, G. A., and Kauvar, A. J. (1941). *New Engl. J. Med.*, **225**, 283.
Hutchinson, J. (1890). *Arch. Surg. (London)*, **1**, 323.
Jennings, G. H. (1938). *Lancet*, **1**, 424.
Johnson, R. J., Harley, R. D., and Horton, B. T. (1943). *Amer. J. Ophthal.*, **26**, 147.
Justin-Besançon, L., Klotz, H. P., Rubens-Duval, A., and Sikorav, H. (1948). *Sem. Hôp.*, *Paris*, **24**, 863.
Kilbourne, E. D., and Wolff, H. G. (1946). *Ann. intern. Med.*, **24**, 1.
Lucien, M., Mathieu, L., and Verain, M. (1939). *Arch. Mal. Coeur.*, **32**, 603.
MacDonald, J. A., and Moser, R. H. (1937). *Ann. intern. Med.*, **10**, 1721.
McKeown, E. F. (1947). *J. Path. Bact.*, **59**, 547.
Meyers, L., and Lord, J. W. (1948). *J. Amer. med. Ass.*, **136**, 169.
Murphy, J. R. (1942). *N.Y.St. J. Med.*, **42**, 2236.
Oldberg, S. (1942). *Nord. Med.*, **16**, 3213. (Quoted by Andersen.)
Paviot, J., Chevallier, R., Guichard, A., and Damez, M. (1934). *Lyon. Med.*, **154**, 45.
Plaut, A. (1942). *N.Y.St. J. Med.*, **42**, 346.
Profant, H. J. (1944). *Ann. Otol. R., etc., St. Louis*, **53**, 308.
Rich, A. R., and Gregory, J. E. (1943). *Bull. Johns Hop. Hosp.*, **72**, 65.
Robertson, K. (1947). *Brit. med. J.*, **2**, 168.
Schaefer, C. L., and Sanders, C. E. (1942). *Amer. Heart J.*, **24**, 410.
Schmidt, M. (1930). *Brain*, **53**, 489.
Schultz, A. (1922). *Virchows Arch.*, **239**, 415.
Scott, T., and Maxwell, E. S. (1941). *Internat. Clinics*, **2**, 220.
Shannon, E. W., and Solomon, J. (1945). *J. Amer. med. Ass.*, **127**, 647.
Sjövall, B., and Windblad, S. (1944). *Acta path. microbiol. scand.*, Suppt., **54**, 385.
Sprague, P. H., and MacKenzie, W. C. (1940). *Canad. med. Ass. J.*, **43**, 562.
Sproul, E. E., and Hawthorne, J. J. (1937). *Amer. J. Path.*, **13**, 311.
Sproul, E. E. (1942). *N.Y.St. J. Med.*, **42**, 345.
Ssolowjew, A. (1924). *Virchows Arch.*, **250**, 359.
Thévenard, M. (1939). *Bull. Mem. Soc. Chirurgiens, Paris*, **31**, 136.
Wagener, H. P. (1946). *Amer. J. med. Sci.*, **212**, 225.