GIANT-CELL ARTERITIS, OR ARTERITIS OF THE AGED

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Giant-cell arteritis, once believed to run a benign course, kills or maims a number of those afflicted, and when in remission it may only sleep. We hope for wider recognition of this common disorder, which is treatable for the most part, but if untreated may progress slowly with pain, palsy, blindness, deafness, and madness in its train, or sometimes more rapidly to a fatal termination. Diagnostic failure is due to many diverse presentations, some of which are little known, and to continued acceptance of a too rigid profile of the disease, despite the fact that the literature is replete with clinical and pathological evidence of its systemic nature. It must be emphasized that classical involvement of the temporal arteries may appear late, transiently, or possibly not at all during the period of observation; it is only one incident of a disorder phased in time and widespread in its distribution.

Hutchinson (1890) and Horton *et al.* (1932) must each be credited for giving temporal arteritis its entity. Gilmour (1941) extended the concept of the disease by pointing out that other arteries were often involved —namely, aorta, internal and external carotids, iliacs, coronary, occipital, and retinal arteries. Cooke *et al.* (1946) drew attention to "a widespread arterial disease, not uncommon, but rarely recognized," and brought the total number of case reports at that time to 37; their own cases, and others already published, illustrating well the poorer prognosis of the disorder. For economy of space, and as the object of the present article is a clinical study of 76 patients, the reader is referred for pathology to papers by Gilmour (1941), Cooke *et al.* (1946), Cardell and Hanley (1951), Heptinstall *et al.* (1954), and in particular those by McCormick and Neubuerger (1958) and Crompton (1959), which illustrate the impact of the disease on the smaller intracranial and meningeal vessels.

The precise relationship, if any, of this generalized arteritis of the aged to thrombo-angiitis obliterans, polyarteritis nodosa, "pulseless disease," and other "arteritic" states has yet to be determined. It is probable, however, that some patients with "aortic arch syndrome" (Gilmour, 1941; Bruce, 1950; McMillan, 1950; Ross and McKusick, 1953; Barker and Edwards, 1955; Harrison and Harrison, 1955) may be suffering from arteritis. It is also probable that thrombosis of the internal carotid artery in some patients arises from the same cause (Meneely and Bigelow, 1953). Extensive atheroma may coexist with arteritis, and, although the precise relationship of each to the other is yet unknown, nevertheless the effect is that atheroma frequently obscures the diagnosis, and so may hyperpiesis. A further complication in diagnosis, but of possible aetiological significance, is the fact that most of our patients gave a history of migraine or vascular headaches since their youth.

Bagratuni (1953, 1956) described the disorder he termed "anarthritic rheumatoid disease"; at that time one of us (Paulley, 1956) expressed the opinion that this condition was none other than temporal arteritis in one of its several guises. Clinical material collected since has supported this view.

Modes of Presentation

1. *Classical "temporal arteritis"* presents with severe head pains rather than headaches, and tenderness over the course of the temporal and occipital arteries, which may be reddened, thickened, and non-pulsatile. The patient is often febrile, with failing vision or blindness of recent origin in one or both eyes. Diplopia, ptosis, and oedema of the face and orbit occasionally occur. The fundi may show papillitis, avascular segments in the retinal arteries, perivasculitis giving the appearance of "sheathing" of the vessels, and exudates. Optic atrophy commonly follows thrombosis of the central retinal artery of its branches, or of the ophthalmic artery. Thrombosis of the retinal veins may also occur (Lander and Bonnin, 1956; Crompton, 1959; Ross Russell, 1959). "Anarthritic" rheumatism especially (see No. 7) and polyarthritis are frequent precursors, by months or years, and may not be mentioned unless specifically asked about. A raised E.S.R. is nearly always present, but by the Wintrobe method it was normal in five of our patients; the Westergren reading in one of these was 85 mm., and she was not anaemic. This is the method we now use. Electrophoresis often demonstrates increases in globulin fractions, especially alpha 2 and beta. Hypochromic anaemia and leucocytosis are frequent. Blood W.R. should be ascertained in all patients, and C.S.F. W.R. wherever possible in those with mental or neurological symptoms. Arterial biopsy is unnecessary in the classical disease, the diagnosis being self-evident, and if the presence of giant cells is made an absolute criterion of diagnosis it may even be misleading; intimal thickening, cellular infiltration, and thrombus formation being more constant findings.

2. *Head pains and headache and tenderness without classical stigmata.*

3. *Facial Neuralgia.*—Cases will be missed if red, pulseless, temporal arteries are insisted upon in diagnosis. More important is a history of severe pains in the neck, occiput, jaw, face, and head, of a type not previously experienced, with extreme tenderness, so that even the pressure of the head on a pillow is unbearable. The temporal and occipital arteries may not be involved at this stage, and we have seen instances where the disease has already dealt its blow to the temporals, leaving them recanalized, or painless fibrous strands. A negative temporal-artery biopsy, therefore, does not exclude the disease, because the vascular changes are patchy and subject to phases of activity (this is well illustrated by Cases 6, 12, and 15). Examination of the internal carotid and facial arteries should always be carried out; some patients show fusiform aneurysmal changes at the bifurcation (Pearse and Hinshaw, 1956) (see also Case 7), where thrombosis may supervene. Facial artery biopsy is sometimes more useful than biopsy of a temporal artery (see Cases 1–5).

4. *Madness (confusion, depression, dementia).*—Minor degrees of this disease are common in its classical form, but it is not sufficiently realized that severe mental changes may predominate, and be the only apparent

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symptom. Many such patients must go undiagnosed to mental hospitals because this potentiality of the disease is not widely known. We have been able to find only one reference in the psychiatric literature (Vereker, 1952), though that author refers to several other articles in which mental symptoms were prominent. The reports by McCormick and Neubuerger (1958) and Crompton (1959) explain very clearly why mental symptoms are common by showing the widespread involvement of the intracranial and meningeal vessels. (See Cases 2, 6, and 7.)

5. *Visual.*—Blurred vision, partial loss of a visual field, transient blindness, or blindness should arouse suspicion of arteritis, and may be so obtrusive as to cause the patient to suppress other symptoms. Birkhead and Wagener (1957) record that 22% of 250 cases in the literature were rendered blind in both eyes, and they point to the 50–75% reduction in the incidence of blind eyes in steroid-treated patients. This presentation is well recorded in the ophthalmological literature, and constitutes one of the disease's worst hazards. (See Cases 2, 4, and 14).

6. *Cardiac Ischaemia.*—If coronary artery disease occurs as a complication of temporal arteritis, as is well known (Gilmour, 1941 ; Cooke *et al.*, 1946 ; Cardell and Hanley, 1951 ; Frangenheim, 1951 ; Morrison and Abitbol, 1955), it is logical that it may sometimes present in this way, but this as yet is rarely considered. Suspicions that a cardiac infarction may be a presenting manifestation of arteritis of the aged (or for that matter disseminated lupus erythematosus or polyarteritis nodosa, which require exclusion) arise when fever persists beyond the usual 7 to 10 days for no detectable cause, and where the E.S.R. remains high for weeks, or months, after the episode of infarction, and if the electrophoresis pattern is abnormal. (See Cases 8 and 15 ; and Case 12, third admission.)

7. *"Anarthritic" Rheumatism.*—Pains and stiffness in muscles of shoulders, arms, back, and legs (Bagratuni, 1953, 1956 ; Paulley, 1956). We suggest that this syndrome is none other than arteritis, in which the classical stigmata of the disease have yet to develop, or have already occurred. (See Cases 12–14.)

8. *Pain in Ear, Vertigo, Deafness.*—There are case reports in the literature of vertigo and deafness (Cooke *et al.*, 1946 ; Kendall, 1953). In our series we have two examples of pain in the ear lasting a few days, with severe vertigo and sudden deafness as the presenting symptoms ; in one of these the other ear was similarly affected a few weeks later, leaving the patient stone deaf. She first came to our notice a year afterwards with episcleritis, malaise and low fever, vertigo, weight loss, and "muzzy"-headedness ; all symptoms except deafness responded to steroid treatment. The pain and suddenness of the aural symptoms suggest a vascular lesion affecting the auditory apparatus, possibly in the same way that the optic nerve is involved by arteritis of the ophthalmic artery (Lander and Bonnin, 1956 ; Crompton, 1959). (See Cases 4 and 10.)

9. *Strokes.*—A few patients presented with strokes. The literature on temporal arteritis records patients having died of strokes (Cardell and Hanley, 1951), but at the time such events were often thought to be unrelated. Though all our patients with cerebral thrombosis had other symptoms and signs of arteritis, these tended to be overshadowed by the major catastrophe, and to be overlooked unless sought for.

10. *Vomiting and Cachexia Suggesting Neoplastic Disease.*—On two occasions patients were referred as probable advanced cases of carcinoma. Both patients were wasted, and were vomiting most of their meals. Generalized limb and back pains suggested widespread skeletal metastases. Vomiting occurred twice in our series when steroid dosage fell too low. (See Cases 8 and 10.)

11. *Masquerading as Meningeal Irritation or Subarachnoid Haemorrhage* (Keen, 1950).—These patients present with severe pains and stiffness in the neck and occiput, but are without abnormal vessels on clinical examination. In spite of the fact that Kernig's sign is usually negative, they require lumbar puncture, and the C.S.F. protein may be raised, usually without an increase in cells. (See Cases 2 and 3.)

12. *Pyrexia of Unknown Origin.*—Another clinical presentation is fever of unknown origin, as seen, for example, on the second admission of Case 8 and as a predominant symptom at the time of admission in Cases 5, 6, and 9.

13. *Polyarthritis.*—Polyarthritis of the rheumatoid type, with frozen shoulder, also occurs, but is perhaps less common than the anarthritic type of rheumatism.

14. *Aortic Arch Syndrome.*—At the risk of being controversial we suggest that arteritis should be thought of as a possible cause in patients with occlusive disease of the aorta and its main branches, and in dissecting aneurysms of the aorta (McMillan, 1950) ; this is borne out by Cases 7 and 11, and by the articles referred to earlier.

Discussion

Series.—From 1953 to 1959 we recognized and treated 76 patients with arteritis of the aged (see Table). Their ages ranged from 54 to 88 at the onset. 75 were followed up ; 8 are dead. Many were missed in the earlier period of study because of failure to recognize atypical presentation.

Nomenclature.—We suggest the possible use of the term "arteritis of the aged" in an attempt to convey the systemic nature of the disease. There are some objections to "giant-cell arteritis" because giant cells are not always present in the smaller vessels. It must also be admitted, however, that not all sufferers are very old.

Psychosomatic Factors in Aetiology.—A depressive state, often concealed, invariably precedes the somatic manifestations of the disease by a few weeks or months and commonly arises from the death or marriage of a near or dear one. However, deaths of cats and dogs were provocative on two occasions in this series. Deprivation other than by death—as, for example, by admission of a beloved person to hospital, especially mental hospital—occurred in a number of our cases. Marriage of sons or daughters incurring separation, especially emigration, and ungracious treatment by relations of recently bereaved old people were recurrent features. The types of stress precipitant, and the personality make-up, are not at present distinguishable from those found by one of us (J. W. P.) in most collagen diseases, particularly rheumatoid arthritis.

Anarthritic Rheumatism.—No proof is advanced that all cases hitherto described are identical with arteritis of the aged, but the circumstantial evidence is in favour. Anarthritic rheumatism as Bagratuni described it, and

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the prodromal rheumatism as seen in our patients, appear to be the same. In arteritis of the aged the rheumatic phase may be prolonged, and usually precedes other symptoms by weeks, months, or years, but it may succeed them. There are occasional examples of dramatic shift of symptoms, from incapacitating rheumatism to cranial manifestations overnight, as in Case 14 and another of our patients.

Diagnosis

In a recent series reported by Ross Russell (1959) diagnosis was made in most cases on clinical grounds; biopsy was done in 11 out of 35 cases. In the present series it was done in 23 out of 76 cases. With increasing experience it now seems an unjustifiable procedure in the very elderly, who are so often unwilling to enter hospital. The small segment of artery available to the histologist, the patchy nature of the disease, its phases of activity, the fact that ophthalmic, intracranial, and meningeal vessels may be more heavily involved than vessels easy of access (McCormick and Neubuerger, 1958; Crompton, 1959) at once place a limited value on temporal-artery biopsy as an absolute criterion of diagnosis. Facial-artery biopsy has sometimes been helpful, and we tentatively suggest that biopsy of the spinal meninges in those patients with stiff backs and necks might be rewarding as a research method if the opportunity ever offered. Random scalp biopsy and muscle biopsy have been unhelpful in atypical and anarthritic rheumatoid patients in this series.

In cases presenting with predominant involvement of the aorta, coronary, carotid, intracerebral, meningeal, ophthalmic vessels, and those of the auditory apparatus, biopsy proof is obviously impossible during life. It is our contention that a clinical diagnosis is justified if one appreciates the natural history of the disease, the recorded necropsy reports (see references), the symptoms, signs—especially in the eye—and the laboratory findings in the form of a high E.S.R. and abnormal protein electrophoresis. On this basis a trial of treatment during life without positive biopsy is preferable to the risk of madness, blindness, or death.

Treatment

Other studies have shown how essential treatment with steroids is in this disease (Whitfield *et al.*, 1953; Harrison and Harrison, 1955; Birkhead and Wagener, 1957; Ross Russell, 1959). Occasionally large doses of prednisone, such as 30 mg. t.d.s., are needed to control the acute stage of the disorder; usually 10 mg. b.d. is effective, but twice in this series A.C.T.H. has controlled the disease where prednisone was only partially successful.

As in rheumatic fever, rapid "tailing" is dangerous and relapse is frequent. A few patients have been successfully "tailed off" steroids after 6 to 12 months and have not relapsed over a period of observation of two to three years, and it may be that several of our more recent cases will eventually join this group. We have sufficient evidence, however, to show that maintenance on steroids indefinitely is beneficial for some patients.

It seems wise to try to discontinue steroid therapy after 6 to 12 months (with a preference for the longer period) and subsequently to observe the patient for signs of clinical relapse, raised E.S.R., anaemia, or fever.

If some emphasis has been laid on psychosomatic factors it is because their evaluation, though admittedly

Details of Series; 76 Patients (36 Male, 40 Female)

Age 80+	70–79	60–69	50–59	Widows	Widowers	Single	Stress Related to Onset	Presenting with Eye Symptoms
12	30	29	5	20	12	8	70 (70)	30

Referred from Eye Dept.	Obliterative Arterial Disease of Eye	Obliterative Disease of Veins of Eye	Presenting with Classical Temporal Arteritis	Presenting Atypically with Head Pains and/or Facial Pains but without Abnormal Vessels to Feel
13	28	2	32	31

Mental Symptoms Prominent	Mental Symptoms Predominant	Presenting with Cardiac Infarction or Angina Pectoris	Presenting with Cerebral Thrombosis	Meningeal Irritation	Dissecting Aneurysm of Aorta
35	12	9	8	3	2

Anarthritic Rheumatism	P.U.O. Presenting Problem in Diagnosis	No. Followed Up, 75		Mode of Death				
		Alive	Dead	Left Heart Failure	Cardiac Infarction	Cerebro-vascular Accidents	Dissection of Aorta	Uraemia
32	16	67	8	4	3	2	1	1

Effect of Treatment with Steroids (No. Treated, 73)				3 Untreated Patients (Female)		
Excellent	Good	Moderate	Poor			
51	12	6	3	Temporal artery biopsy 1954. Remitted. Remains well	Diagnosed 1956. Chronic ill health. Anaemia, head pains, vertigo, rheumatism. On and off since	Classical temporal arteritis 1959. Remitted spontaneously. Remains well under observation

Relapses on Reduction or Cessation of Steroids	Clinical Features and Investigations						
	Fever 100° or More	Anaemia Less than Hb 80%	Raised E.S.R. (Wintrobe)	Abnormal Protein Electrophoresis	Artery Biopsy Done	Positive	Giant Cells Present
29	30	23 (62)	67 (72)	28 (34)	23	21 (23)	10 (23)

Totals do not tally because of multiple presentations, and multiple admissions in a few patients with different presentations, as in Mrs. F and Mr. L
Figures in parentheses indicate the number of patients involved where this is less than the whole series of 76.

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controversial in aetiology, has been found of considerable importance in treatment. In our experience, relapse is unlikely where the provocative emotional stress is non-recurrent; but where these old people have to live in an unrelieved stressful situation, or have been unable to accommodate, doctors need to be vigilant, and steroids may have to be maintained for a long time. What the level of maintenance should be is a matter for individual determination; prednisone, 5 mg. once or twice daily, appears to be too low initially. Most cases remain well on 12.5, 15, or 20 mg. of prednisone a day. Skeletal osteoporosis has to be looked for during long-term treatment and countered by suitable oestrogen and androgen preparations and calciferol. To date we have not had complications from intercurrent infection. Vomiting or refusal to take steroids should be immediately reported; this constitutes an emergency about which patients, their relatives, and doctors should be warned.

Because of the smouldering nature of the disease, and the severity of its complications, we advise the closest supervision of patients in apparent remission.

We give below the history of 15 cases; the Table on p. 1564 correlates details of the series.

Case-histories

Case 1.—In October, 1959, Mrs. A, aged 62, presented with malaise, nausea, excruciating pains in right face, temple, and occiput for five weeks; temperature 99–100° F. (37.2–37.8° C.); she became aware of tender spots on scalp, but none were visible or palpable. Facial, occipital, and temporal arteries normal. E.S.R. 35 mm./hour. Electrophoresis, α_2-globulin increased. Hospital admission not sought; the diagnosis being evident, she was treated with prednisone, with an immediate response. A month later, a mild relapse on dose being reduced to 5 mg. b.d.; she remained well on 5 mg. t.d.s.

Case 2.—Miss B, aged 63. Nervous breakdown in 1956 after domestic discord. Central retinal venous thrombosis occurred shortly afterwards—a recognized eye manifestation of arteritis. Admitted September 8, 1959, for suspected meningitis or subarachnoid haemorrhage with a three-weeks history of neck stiffness, occipital pain; finally, fever 100° F. (37.8° C.) for two days, drowsiness, dysarthria, and mental confusion. Examination revealed no abnormal vessels. C.S.F. and blood W.R. negative. E.S.R. 48 mm. Hb 89%. No L.E. cells. Plasma protein globulin 4 g.%, increase in α_2. Immediate response to predisone 10 mg. t.d.s. in 12 hours. She stated the morning after admission: "It's floated away; it's just like heaven." Dysarthria and full mental faculties took about a week to recover.

Case 3.—Mr. C, aged 80, was depressed after his wife's long illness and death. He had occasional headaches; with increasing unhappiness in his environment, however, in November, 1957, he suddenly developed severe temporal and occipital headache, and was unable to bear pressure of head on pillow. Mental confusion began to occur at night. Superficial scalp vessels normal to feel, occipital tenderness was present. B.P. 180/100. E.S.R. 9 mm./hour Wintrobe. W.R. negative. Being unwilling to enter hospital he was treated with prednisone and lost his symptoms in 24 hours. Three months later he stopped taking prednisone against advice, fearing addiction. Headaches recurred. Subsequently prednisone was taken only when he had headaches, as if it were aspirin. Mental confusion did not recur, but he died elsewhere of cardiac infarction in September, 1958, after several lesser heart attacks.

Case 4.—Mr. D, aged 67, had lost his wife and took to drink; he was seen in September, 1958. Had had sudden pain in right side of head and ear a year before, followed by giddiness and deafness on that side. Memory deteriorated and he was unable to concentrate or do his job properly. Deafness persisted. During summer of 1958 he had transient attacks of blindness in left eye; ophthalmological opinion was that temporal arteritis should be considered, the fundus being avascular and the vessels showing considerable irregularity. B.P. 170/90. E.S.R. 32 mm./hour. Hb 86%. W.B.C. 5,000. W.R. negative. Prednisone 5 mg. q.i.d, with immediate improvement mentally, and he was able to work normally. No further attacks of transient visual losses, but some deterioration of memory and concentration on dose of 5 mg. b.d. Symptoms again remitted on 5 mg. q.i.d. (October, 1959).

Case 5.—Mrs. E, aged 70, a depressive, jealous widow, with a domestic situation full of strife, was referred in April, 1958, for P.U.O. and malaise. Direct questioning produced a story of intense pains in head, neck, and jaws, beginning four months previously; had had to hold her head in her hands all night. When seen she had had no pain for three weeks. Night temperature 100° F. (37.8° C.). Hb 54%. E.S.R. 45 mm. Wintrobe (corrected). Cranial vessels appeared normal, but pigmentation was observed over the course of temporal arteries. She told of a sensation like "egg-shell crackling" when she had touched her temples some weeks before. There was immediate response to prednisone, and she remained well on a maintenance dose of 5 mg. b.d.

Case 6.—Mrs. F, aged 68; admitted April 26, 1955, with three weeks' history of pains of great severity in neck, jaws, and both sides of face, backache, vomiting, poor memory, confusion, and disorientation. She had had vertigo four years previously. She was very worried by a "simple" sister who had lived with her three months and needed constant supervision. A psychiatrist advised immediate admission to mental hospital with diagnosis of "paraphrenia with delusions and hallucinations." When seen by one of us on the same day, she was wild-eyed and in great pain, sitting up with her face in her hands. She was able to point to the tender areas over the facial, temporal, and occipital arteries, which were grossly thickened. Biopsy positive. W.R. negative. Hb 73%. E.S.R. 38 mm. Immediate return to "sanity" on cortisone 25 mg. q.i.d. in 24 hours, and relief of pain. After six months' maintenance on cortisone 50 mg. b.d. she was "tailed off" gradually. On February 6, 1956, she was readmitted as an emergency, complaints then being lassitude, insomnia, slight occipital headache, and three weeks' fever at nights. 99–100° F. (37.2–37.8° C.). On examination the most notable feature was mental apathy; there were no abnormal superficial vessels. E.S.R. 36 mm. Hb 58%. W.B.C. 9,300 (polys 84%). B.P. 110/70. Immediate response of all symptoms and fever on reintroduction of cortisone. Her own doctor then kept her on a maintenance dose of cortisone, but by November, 1959, she was having only 12.5 mg. a day. In October, 1959, her daughter was admitted to a mental hospital to patient's great distress. Three weeks later she followed her daughter to the mental hospital with precisely the same clinical presentation as in 1955, but no abnormal vessels were to be found. Prednisone 20 mg. t.d.s. was needed to bring this episode under control in a week.

Case 7.—Mrs. G, aged 72, attended on October 21, 1959. For six weeks she had had stiffness and soreness of shoulders, hips, knees, and ankles, with swelling of the latter. For weeks previously she had pains in the neck and, at the outset, sweats. Mild frontal and occipital headaches had been present for six years. She had been "losing herself" since onset, imagining things that had not happened and having no memory for recent events. For two weeks she had been somnolent. Examination revealed so slight a degree of redness and thickening of the left temporal artery as to have normally escaped attention. Biopsy positive. There was aneurysmal dilatation of bifurcation of left common carotid, aneurysmal dilatation of aortic arch with inner ring of calcium, aortic incompetence; B.P. 200/115. Fundi—no papilloedema, arterial irregularity, and exudate and a haemorrhage (right). Hb 65%. W.B.C. 8,200 (polys 83%). E.S.R. 33 mm. Electrophoresis: globulin 3.4 g.%; increase in α_2-globulin. L.E. cells negative. C.S.F. normal.

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W.R. negative The patient was febrile, 100° F. (37.8° C.), and very confused. Prednisone, 20 mg. q.i.d. for a few days, and then reduced, produced dramatic recovery, enabling her to return home on November 10 on prednisone 10 mg. b.d. Her husband's last report is that "she is sensible and doing her housework; her relatives are amazed." The family thought her depression was due to the admission of a favourite niece to a mental hospital a few weeks before onset.

Case 8.—Mr. H, aged 86, admitted on November 12, 1956. Referred for suspected carcinomatosis. In 1954 he lost his wife unexpectedly from pulmonary embolism and became depressed. In April, 1956, he consulted his doctor because of dyspnoea and palpitations. Auricular fibrillation was present. Subsequent E.C.G. suggested that he had had a silent cardiac infarction. He said he had felt tired ever since his wife's death, and for several months had had pains up his back, pain and weakness in legs making walking difficult, nausea, anorexia, loss of weight, stiffness in the mornings "all over," and "pain in jaw on chewing." Examination revealed a thrombosed right facial artery. Biopsy positive. E.S.R. 27 mm. B.P. 180/80. W.B.C. 8,000 (polys 78%). Immediate and dramatic response to cortisone 25 mg. q.i.d. Maintained since on 25 mg. b.d. He remains well.

Case 9.—Mr. I, aged 68, admitted on March 23, 1956, for P.U.O. Night temperature 101° F. (38.3° C.); depression for three months. A history of sharp head pains at the outset had to be dragged out of him. Hb 56%. E.S.R. 30 mm. Temporal artery biopsy positive. Immediate response to cortisone. Remains well; off steroids two years.

Case 10.—Mr. J, aged 75; admitted on November 6, 1956. Referred with diagnosis of carcinomatosis and heart failure. Vomiting and loss of weight were presenting features of a few weeks' duration, and swelling of legs for two months. Five months previously he had had severe pains in left leg and in his shoulders, then spreading all over him, including his head. He also complained of a "frog" in his ears, and tinnitus, smarting eyes, and dizzy spells. His gait had been unsteady. He lived alone since his wife's death in 1949, but had become very depressed after recent death of a son-in-law. Temporal arteries were red, thickened, non-pulsatile, and visible from the door; biopsy was done, but was technically unsatisfactory. E.S.R. 32 mm. Hb 74%. W.B.C. 5,200 (polys 78%). C.S.F., increase in globulin. W.R. negative. Cortisone 25 mg. q.i.d. brought relief of all symptoms. Maintenance on 25 mg. b.d. was stopped in November, 1957. He has remained in excellent health since without steroids.

Case 11.—Mrs. K, a widow aged 70, had had headaches all her life. In August, 1957, intensity of head pains increased in left temple, with blurring of vision a month later. In October she had bilateral papilloedema, and the left temporal artery was nodular and non-pulsatile. A diagnosis was made elsewhere of arteritis of temporal and retinal arteries by an eminent physician. Biopsy was refused. E.S.R. 49 mm. Urine: R.B.C., polys, urea 37 mg./100 ml. W.B.C. 10,000 (polys 71%). B.P. 230/120. W.R. negative. A few months later she developed a large dissecting aneurysm of the arch and descending aorta. She died in her sleep in September, 1958. Prednisone relieved her headache, but she developed increasing signs of heart failure after her aortic catastrophe.

Case 12.—Mr. I, aged 69, was admitted on February 1, 1954, with pain and stiffness in shoulders, back, thigh, calves, and right wrist for six weeks. Retired manager (three years); wife died 16 months previously. He had had a shock when a sister with whom he was staying died suddenly at Easter, 1953. Depressed by unhappy relationship with daughter. He was febrile 99.2° F. (37.3° C.). E.S.R. 30 mm. Hb 78%. B.P. 180/85. Rheumatoid arthritis was diagnosed. He responded immediately to cortisone and mobilization; the drug was tailed off over two weeks, being followed by a short course of A.C.T.H. and physiotherapy as out-patient. By April 16 he had relapsed. Readmitted on May 27 with temporal headaches, and had seen an eye specialist because of sudden pain in left head and deteriorating vision in left eye. The left disk showed a papillitis and some exudate. V.A. 6/36. Left temporal artery tender, thickened, but pulsating. Diagnosis, temporal arteritis. Treated with cortisone for three weeks and then A.C.T.H. for seven days, with recovery. On February 20, 1956, emergency admission with cardiac infarction after three months' lethargy, and angina of effort. Died.

Case 13.—Mrs. M, aged 68, a depressive, martyred widow, distressed over recent emigration of her son and marriage of her daughter to a foreigner, attended as out-patient on November 16, 1959, with a history of aching legs for two years. Her back became affected in August, 1959: "like being in a plaster cast." When seen she had pains in shoulders, back of legs, and for one week violent pains up the back of her neck—"to drive me crazy"; unable to move unassisted. No temporal or jaw pain, but "muzzy-headed" at times. Tender over upper dorsal spines, nowhere else. Stiff neck and shoulders and back. B.P. 160/80. Febrile 100° F. (37.8° C.). Hb 84%. W.B.C. 13,400. E.S.R. 40 mm. Electrophoresis: globulin 4.4 g.%; increase in α_2 and β fractions. L.E. cells negative. Blood culture sterile. Skeleton normal. Immediate complete response to prednisone; now on maintenance 5 mg. t.d.s.

Case 14.—Mrs. N, aged 70, was seen on January 7, 1959. Fifteen months previously, after retirement from work, and the death of her cat by poisoning, she became depressed. Rheumatic pains in knees, back, and shoulders quickly followed. She was severely disabled. One morning in November, 1958, she woke to find all her rheumatism gone, instead she had pains in her head and jaw. Three weeks later she had diplopia and then blindness in her left eye. She had tinnitus and had been stumbling and veering to the right for five months; was anaemic, had lost weight, and was losing vision in her remaining eye. Clinically, she had classical temporal arteritis, with bilateral papillitis and absent left light reflex; the left eye was quite blind. Hb 75%. E.S.R. 26 mm. W.B.C. 6,600 (polys 68%). Normal plasma globulin. There was a good response to prednisone 10 mg. t.d.s., and the right eye recovered. She remained well on prednisone 5 mg. b.d. She presents an example of the way this disease appears to switch its point of attack—sometimes, as here, literally overnight.

Case 15.—Mr. O, aged 65; admitted on May 5, 1959, with sudden ischaemic chest pain. E.C.G. confirmed anterior cardiac infarction. S.G.O. transaminase 90 units. After three weeks of persistently raised temperature, and with E.S.R. 34 mm., basal crepitations, electrophoresis globulin 4.4 g.%, with all fractions increased; polyarteritis nodosa suspected, but skin and muscle biopsy and L.E. cells negative. Immediate response of signs and symptoms to prednisone 5 mg. t.d.s. Discharged on maintenance dose of steroids, but these were stopped for some reason after five weeks. Within a fortnight he was admitted to another hospital with classical temporal arteritis. The clinicians there were surprised by a negative biopsy, but their faith in the diagnosis remained unshaken.

Summary

Seventy-six patients with arteritis of the aged (giant-cell arteritis) have been seen since 1953, approximately half of them in the last 12 months.

Case-histories have been selected to illustrate the lesser known presentations of a common disease which we believe must often confront psychiatrists, rheumatologists, neurologists, cardiologists, vascular, E.N.T., orthopaedic surgeons, and geriatricians, not to mention ophthalmologists, who are perhaps most aware of it, and general practitioners and physicians.

When elderly people begin to fail mentally or physically this should be one of the first disorders to be considered, and not one of the last.

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MODE OF ACTION AND SIDE-EFFECTS OF PHENFORMIN HYDROCHLORIDE

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The hypoglycaemic action of phenformin hydrochloride (phenethylbiguanide; "dibotin"; D.B.I.) has been observed in all types of diabetes. It has been the cause of some concern that its use can be associated with the appearance of ketonuria and acidosis in the presence of normal or slightly elevated blood-sugar levels (Hall *et al.*, 1958; Steiner and Williams, 1959). This occurs chiefly in the juvenile diabetic (Walker and Linton, 1959a). It is uncertain whether this anomaly is specifically caused by D.B.I. or whether it is due to absolute or relative lack of insulin. The object of this paper is to report some clinical features of the acidosis and to relate them to the present hypotheses of action of D.B.I.

Clinical Observations

Observations were made on a series of 109 diabetics of all types controlled on D.B.I. either alone or with supplementary insulin. Good control was often obtained, as judged by the accepted criteria. The results of part of the series are reported elsewhere (Walker and Linton, 1959b). Interest was drawn to the occurrence of ketonuria in the presence of normal or only slightly elevated blood-sugar levels. It was found that ketonuria was accompanied in 11 cases by frank reduction in alkali reserve.

It will be seen from Fig. 1 that a severe fall in alkali reserve was virtually confined to juvenile diabetics, although ketonuria appeared in all types. This seemed important and was thought to be related to the basic difference between adult and juvenile diabetes—that is, the presence or absence of endogenous insulin (Wrenshall and Best, 1956). It was then observed that there was an association between the appearance of acidosis and the amount of exercise taken. Close inquiry confirmed that any moderately severe physical exercise tended to produce ketonuria and acidosis in juvenile diabetics on D.B.I. It was further observed that the fresh urine from the patients on D.B.I. alone had a *p*H of less than 5.6, while the urine of other diabetics almost without exception exceeded this.

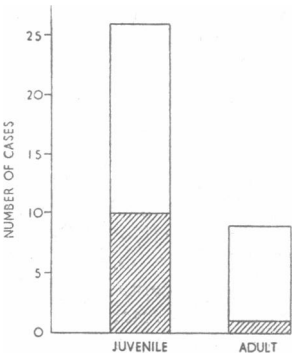

FIG. 1.—Incidence of ketonuria with or without acidosis in 102 cases. White columns = Ketonuria alone. Hatched columns = Ketonuria with acidosis. (Acidosis = alkali reserve below 20 mEq/l.) Note: "Juvenile" includes two juvenile-type adults with acidosis.

About this time the urgency of the problem was emphasized by the occurrence of two cases of very severe acidosis among the patients on D.B.I. (Walker and Linton, 1959a). Both were admitted to hospital in what appeared to be a diabetic coma. Case 1 had a blood-sugar level of 208 mg./100 ml. and an alkali reserve of 4.9 mEq/l. In Case 2 the respective values were 280 mg./100 ml. and 3.1 mEq/l.

The latter patient died despite strenuous empirical measures—intravenous glucose, insulin, and alkali—designed to combat acidosis. In neither case was there any obvious predisposing factor, and in both cases the biochemical upset was rapid in onset and severe in degree. Case 1 was controlled solely with 100 mg. of D.B.I. daily and is now controlled with 56 units of insulin. Case 2 was having 150 mg. of D.B.I. daily with 12 units of I.Z.S. ("lente" insulin).

A further case which threw some light on the problem was admitted some months later. There was severe acidosis and elevation of blood sugar; D.B.I. had been omitted for two days (blood sugar, 512 mg./100 ml.; alkali reserve, 15.2 mEq/l.) and again empirical methods were used. Insulin was given by intravenous and intramuscular routes, to a total of 280 units in the first 12 hours. In the first four hours, while blood sugars fell in the anticipated way, the alkali reserve deteriorated, reaching 5.8 mEq/l.; the alkali administered had been sodium lactate. Thereafter sodium bicarbonate was substituted, and the desired effect was obtained in a sharp rise of the alkali reserve.

Normally, intravenous administration of sodium lactate will result in an increase in the alkali reserve, as the lactate ion is either quickly metabolized in the Krebs cycle or converted to glycogen, leaving the sodium ion free to form sodium bicarbonate. In this case the further metabolism of lactate is probably blocked, and it contributed to the increased pool of lactate which is already present in patients on D.B.I.

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