NEUROLOGICAL COMPLICATIONS IN HYPERSENSITIVITY

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Hypersensitivity state is the altered activity of cells to any foreign substances, a normal physiological phenomenon of protective adaptation. Allergy and hypersensitivity are our saviour for which we should be grateful to nature. Allergy is now being applied commonly to the pathological variants of the physiological process. Allergy, physiologically, allows the organism to react to antigenic substances to neutralize them.

Antigen antibody reaction, in certain people, may end naturally without any after-effects and in others may terminate in pathological process, presumably due to inherent individual constitutional defect and defective enzyme system in certain tissues or defect in the natural process of the immunity with the production of abnormal antibodies, possessing affinity to certain tissues with a capability of injuring them. Identification of antibodies, other than those occurring in streptococcal infection, has not been often established, though some have reported antireticulin, antimycardial and antirenal antibodies.* At the moment we know little about cell-fixed antibodies.

Autosensitization

In certain people, autoimmunization, following autosensitivity to certain endogenous products, might play a part in the production of multiple antibodies. A good clinical example of autoimmunization is found probably in lupus erythematosus, which is presented with haemolytic anaemia in association with circulating antibodies proved by positive Coombs' test, thrombocytopenic purpura, false positive W.R., increase gamma-globulin and multiple antibodies formation following blood transfusion. If lupus is regarded as a disease of autoimmunization, we do not know what antigenic substance is involved nor how it is rendered autoantigenic. Lupus, rheumatoid arthritis, polyarteritis and dermatomyositis differ

from acute and self-limited collagen disease in that the course is protracted over many years, and if they are diseases of hypersensitivity we must postulate that the antigenic substance must be present in the body throughout this long period of activity, probably not being neutralized due to defective process of the immunity. The same can be applied to disseminated sclerosis in which myelin sheath is involved instead of connective tissue.

Hypersensitivity and Collagen Diseases

Pirquet's original concept (1903) of allergy has withstood the test for 50 years and is substantially true today. The clinical manifestations of hypersensitivity now can be classified in four main groups:

1. Asthma, hay fever and infantile eczema.
2. Serum sickness, drug allergy and contact dermatitis.
3. Bacterial and viral allergy (yet in infancy).
4. Autoimmunization, lupus, thrombocytopenia, haemolytic anaemia and hyperfunction of reticulo-endothelial system with auto-antibodies formation (Bywaters, 1956).

There is widespread assumption that collagen diseases are probably due to hypersensitivity (Rich, 1946). Fibrinoid necrosis of collagen, such as seen in acute rheumatism, polyarteritis following infection and serum sickness (Rich, 1946), can also be found in mechanical injury to collagen such as in malignant hypertension, peptic ulcer and acute pancreatitis (Klemperer, 1948). There is no convincing evidence that collagen itself is involved. Klemperer himself now believes that fibrinoid of lupus is probably derived from the breakdown of nucleic acid, supposed to be set in process by gamma-globulin, a serum factor produced during autoimmunization. Gamma-globulin inactivate the desoxyribonuclease inhibitor enzyme and allow nuclear degeneration of leucocytes which consequently is ingested by polymorphs. These deep purple staining bodies are found in

*Globulin fraction on antikidney serum tagged with ¹³¹I is localized primarily in the glomeruli as determined by radioautograph.

connective tissues identified by Klemperer (1948) as desoxyribonucleic acid. The same was found in lupus erythematosus cell and marrow by Har-
 graves *et al.* (1948).

The efficiency of cortisone and ACTH in arresting the disease process in rheumatoid arthritis and lupus may depend upon the ability of these hormonal agents to reverse this destructive enzymatic process in the affected cells rather than upon the unknown cause of the disease. This hypothesis is supported by the prompt effect of the therapy and equally prompt recurrence of illness upon withdrawal of these agents.

Hydralazine (apresoline), used for hypertension, can also produce mesenchymal reaction simulating lupus and rheumatoid arthritic features in association with lupus erythematosus cell phenomenon. These lupus erythematosus cells are also found in penicillin sensitivity and virus hepatitis. Apresoline has a strong affinity to combine with carbonyl and sulph-hydryl groups. Thus we can produce the disease at will in animals and can study its pathology.

Many clinical and pathological features are common to all collagen diseases, with some variation in intensity and distribution. Hypersensitivity is a common factor to all. Disease may start with one syndrome predominating; as it progresses, this is replaced by another. In each case cellular infiltration and fibrinoid necrosis is associated with lymphoid hyperplasia and gamma-globulinaemia. Increase gamma-globulin is regarded as a response to antigen antibody reaction (Aegerter and Long, 1949; Long, 1954, 1955). The pathology of early stage is unknown. In an experimental analogous disease the earliest lesion, in guinea-pig, is oedema (Long, 1954, 1955), and this is shown in rheumatoid arthritis (Kulka *et al.*, 1955) which is soon associated with cellular infiltration and vascular insult.

Neurological Complications in Hypersensitivity

Mayo Clinic has played an important role in advancing the knowledge of lupus. Clark and Bailey (1956), of the same institute, have drawn attention to the frequency with which mental and neurological complications occur in this disease. They reviewed the neurological complications in systemic lupus observed at Mayo Clinic; these included convulsions, mental disease, hemiplegia, polyneuritis, subarachnoid haemorrhage, vertigo, nystagmus, chorea, monoplegia. Pathological study revealed widespread vascular lesions in the central nervous system. Similar neurological complications have also been observed in poly-
 arteritis.

Involvement of the central nervous system has also been observed in Behcet syndrome (Behcet, 1937, 1939, 1940) and in Steven Johnson syndrome (Ashby and Lazar, 1951) resembling disseminated sclerosis, presenting the same basic pathology as seen in hypersensitivity.

There is a growing evidence to believe that post-infectious perivenous demyelinating encephalomyelitis and post-infective polyradiculoneuritis (Landry-Guillain-Barre syndrome) are allergic reactions. These diseases are manifested 7-14 days following the infection, at a time when antibodies are being formed with a tendency to spontaneous recovery. Miller (1956) believes that these are secondary to the initial vascular insult, probably due to hypersensitivity. This toxic-allergic complication had been for many years the explanation of rheumatic fever and glomerulonephritis following streptococcal infection. In post-infectious neurological disorders there is a damage to the melin sheath, while in the collagen disorders connective tissue is injured. We do not know the exact mechanism of these syndromes of unknown cause.

Clinical Material

The present paper deals with the neurological disorders observed in cases with hypersensitivity manifestations: drug allergy, polyarteritis, systemic lupus, hypersensitivity angitis and post-infection allergy. Twenty-one cases have been observed; signs and symptoms are analysed.

TABLE I		No. of
Diseases		cases
Polyarteritis		3
Schönlein-Henoch allergic vasculitis		1
Hypersensitivity angitis		1
Allergic granulomatous angitis		1
Pulmonary lupus		2
Allergic polyradiculoneuritis		4
Spontaneous acute disseminated encephalomyelitis:		
(a) Myelitis type		3
(b) Encephalomyelitis type		2
Glandular fever syndrome		1
Meningococcal meningitis		1
Drugs allergy		2
		21

TABLE 2		No. of
Hypersensitivity States		cases
Upper respiratory tract non-specific infections	10	
Asthma with eosinophilia (48% in one case) (10% in other case)		2
Meningococcal infection		1
Staphylococcal		1
Streptococcal		1
Drugs allergy		2
Unknown		4
		21

TABLE 3

Neurological disorders	No. of cases
Neuropathies:	
(a) Symmetrical polyneuritis in the legs ..	3
(b) A symmetrical polyneuritis (mononeuritis multiplex) ..	3
Asymmet. polyradiculoneuritis ..	4
Hyper-reflexia followed by areflexia ..	3
Transversemyelitis ..	4
Encephalitis ..	1
Mononeuritis (R. ext. popliteal palsy) ..	2
Convulsions ..	1
	21

TABLE 4

Age in Years	No. of cases	
	Male	Female
0-10 ..	0	0
10-20 ..	3	0
20-30 ..	0	1
30-40 ..	0	4
40-50 ..	3	3
50-60 ..	1	2
60-70 ..	2	1
70-80 ..	0	1

A. Spontaneous Acute Disseminated Encephalomyelitis

A form of acute disseminated encephalomyelitis clinically and pathologically identical with post-exanthematous and post-vaccinal encephalomyelitis may occur following on an influenzal type of febrile illness. McAlpine reviewed the clinical picture and described a cerebral and a spinal clinical type (1931). Miller and Evans (1953) regard this illness as a non-specific allergic reaction of the C.N.S. to various antigens, chiefly bacterial and virus infection, and possibly other kinds as well.

Clinical Features

In the five presented cases onset of the neurological complications was sudden, following a non-specific upper respiratory tract infection, two to three weeks previously, at a time when antibodies are formed.

Case.—Female, aged 45, developed spontaneous acute disseminated myelitis in association with pyrexia 100° F., tachycardia, headache, depression and transverse myelitis. She exhibited unusual hyperalgesia to cold on the left leg. She was showing remissions and relapses of motor paralysis in the legs successively within a short time for two months. These were controlled by a course of ACTH† gel. 40 units b.d. for one week, followed by cortisone 100 mg. daily which was reduced gradually to 12.5 mg. in a six weeks' time, which

†ACTH and cortisone may be dangerous in cases of virus diseases such as polio, bacterial infection of C.N.S. (abscess) and T.B. meningitis. These diseases should be excluded before their administration.

was maintained for a further six weeks. Two months later she was seen when complete regression of the transverse myelitis was found. C.S.F. was normal, except raised proteins up to 50 mg. per 100 ml.

Case.—Female, aged 32, developed spontaneous acute disseminated encephalomyelitis following a non-specific upper respiratory tract infection two weeks prior to the illness, in association with pyrexia 102° F., headache, neck stiffness, diplopia, severe dysarthria, cerebellar ataxia, flaccid limbs without changes in the reflexes and tachycardia. C.S.F. examination revealed normal pressure with raised protein (120 mg. per 100 ml.) and cells (150 mononuclear cells per c.mm.). She was treated symptomatically with complete recovery in six weeks. In such cases pleocytosis is due to meningeal involvement, otherwise proteins are raised and sometimes C.S.F. is normal.

Some cases are presented with hemiplegia, hemianopia, aphasia, convulsions, and focal neurological signs (McAlpine, 1931). Motor weakness in the lower limbs may progress to complete paraplegia as occurred in the above-described first case, in a day or two of the onset, but may be delayed up to three weeks. The way in which fresh neurological symptoms appear, within the first three weeks, but in rare instances up to few months from the onset, as in the first case, is regarded highly characteristic. Mortality rate is low. Recovery is complete, though in some cases sequelae remain. Inclusion bodies encephalitis usually terminates fatally, but may become arrested.

Radicular type of pain in the back was complained by four cases. This is an important characteristic feature of acute disseminated myelitis which differentiates it from disseminated sclerosis.

Headache, fever and tachycardia with absence of euphoria were present in all. Extensive sensory loss to vibration, joint sense, pain temperature with acute paraplegia was noted in four cases of disseminated myelitis which is rarely observed in disseminated sclerosis.

In cases of disseminated myelitis, if residual signs persist after acute stage, then diagnosis from disseminated sclerosis is extremely difficult. The diagnosis is based upon history of onset following infection, characteristic symptoms and absence of any extension of the physical signs after first three weeks of illness. Occasionally disseminated encephalomyelitis and acute disseminated myelitis follow a relapsing course (McAlpine, 1931; Miller and Evans, 1953). This was noted in one case up to two months which was controlled by cortisone and ACTH therapy. Miller (1953) has used ACTH for the treatment.

of acute disseminated encephalomyelitis. McAlpine (1931) has drawn attention to the following points as diagnostic for acute disseminated encephalomyelitis:—

1. A temperature of over 100° F.
2. Severe shooting pain.
3. Absence of euphoria.
4. Loss of pain and thermal sensibility, or diminution of all sensation below the sensory level, or presence of dissociated anaesthesia.
5. Motor weakness in the lower limbs with paraplegia is usually noticed within a day or two of illness, or delayed till the end of two or three weeks. Reflexes are exaggerated or abolished. Fresh neurological signs appear within the first three weeks or delayed up to few months with complete recovery. Sphincter disturbance is common. Ataxia with rapid and fine nystagmus is present. Bilateral optic neuritis with myelitis simulate Devic's disease, which is also observed after measles and vaccination.

The presented five cases were fulfilling the criteria described by McAlpine. Three cases developed paraplegia within two weeks of the onset of illness with extensive sensory loss, and in one case onset was delayed to three weeks and fresh neurological signs were appearing up to two months with paraplegia and extensive sensory loss in the legs.

Aetiology

The development of encephalomyelitis following specific fevers, vaccination and during antirabic treatment has long been recognized. Post-vaccinal and post-infectious neurological complications have an identical pathology. Although this is designated as encephalomyelitis, an infective agent has never been isolated from the central nervous system. Recent experiments with the injections of homologous and heterologous brain tissue with adjuvants (dead tubercle bacilli and mineral oil) produced the pathological picture resembling the post-infective encephalomyelitis and throw doubt on infectious aetiology of the disease (Kabat *et al.*, 1954; Wolf *et al.*, 1947; Lumsden, 1949, 1956). The nature of the antigen and the mechanism of brain damage has not yet been elucidated. Colover (1954-56) and Colover and Consden (1955) have demonstrated that the active agent in the dead tubercle bacilli is an insoluble somatic protein bound compound which is mainly formed of amino-acids with a long chain fatty acid rather than lipid or wax or polysaccharides. The role of adjuvants is described as purely potentiating and it must be given at the same site. Lumsden (1949) also demonstrated that active agent in the injected brain was protein or protein-bound compound rather than a lipid.

Russell (1955) described fibrinoid necrosis of the vessels in acute haemorrhagic leucoencephalitis and polyarteritis type of vascular lesions in acute disseminated myelitis. She also described plasma cells and their precursors in the spleen of both type of cases and concluded that 'allergy' is the basis of reactions in the central nervous system. Campbell and Good (1950) also described plasma cells in the spleen of guinea-pigs with experimental allergic encephalitis. Encephalitis following arsphenamine (Russell, 1937), streptomycin and P. aminosalicylic acid (Cavanagh, 1953) is possibly the result of hypersensitivity. Acute haemorrhagic leucoencephalitis characterized by febrile illness, headache, vomiting, stupor with or without hemiparesis with polymorphonuclear leucocytosis in blood and high cell counts in the cerebrospinal fluid with many polymorphs and signs of acute disseminated encephalomyelitis represent different grades of intensity of reaction to a similar pathological process (Greenfield, 1950; Russell, 1955).

Miller and Evans (1953) believe that acute disseminated encephalomyelitis is the result of non-specific allergic reaction in the central nervous system, to various antigens—bacterial, virus and other kinds. Acute disseminated encephalomyelitis and acute haemorrhagic leucoencephalitis are similar to the experimental allergic encephalitis, post-vaccinal and post-exanthematous perivenous demyelinating diseases, serum sickness, angio-neurotic oedema, glomerulonephritis and purpura (Miller and Evans, 1953). Miller (1956) believes that the neurological disorders are secondary to the initial vascular insult in post-exanthematous encephalitis. Blackwood (1956) concluded that the histopathology is too slender to exclude or confirm allergy in the pathogenesis of post-exanthematous encephalomyelitis.

Recurrence in post-exanthematous encephalomyelitis is unknown and also in illness following specific fevers. If nervous disorder follow a minor non-specific infection of upper respiratory tract, lasting immunity, in such cases, is lacking and repeated such antigenic insults play a part in the pathogenesis of recurrence of neurological disorders (Miller and Evans, 1953). This fact explains the recurrence of neurological disorder in one of the presented cases up to two months. Perhaps this, also, explains the relapses in disseminated sclerosis.

Recently the aetiology of disseminated sclerosis is narrowed down to infection and allergy (McAlpine, 1956). The possible source of infection is the upper respiratory infection to which lasting immunity is lacking. Abrupt onset, relapsing, remitting course, increased globulin in the C.S.F., occasional association with the other form

of allergy and recurrence of the attacks following infection, fatigue, lowered state of general health, trauma and emotional upset favour allergy. Perhaps the silent reactivated allergens or the new allergens, due to the defective immunity, produce fresh crops of antibodies, consequently new lesions are produced in the C.N.S. Autoimmunization seems as good as any at the moment.

Many potential allergic patients who keep good health and live in a favourable environment escape allergic symptoms. They remain in so-called allergic balance, so that their symptoms remain subclinical. Once the natural defences have been lowered by infections, nutritional disturbances, hormonal imbalance stress, marked weather changes, habits, drugs, vaccines and psychosomatic disorders which impair their well-being, allergic manifestations emerge in severe forms, and if not corrected early lead to a crippling invalidism.

In recent studies in U.S.A., Lubens (1955) reports on 300 cases of poliomyelitis, and states that the incidence of bulbarpolio was found to be as much as five times as great among those with an allergic history as among those without such background. The mortality from polio was also greater among allergic than among the non-allergic.

B. Neuropathies and Hypersensitivity

(a) *Polyarteritis Nodosa*

Kussmaul and Maier (1866) described neuropathy in their original case of periarteritis nodosa. Since then the incidence of it, in different series, has varied from 8 to 10 per cent. Kernohan and Woltman (1938) first differentiated the successive involvement of peripheral nerves (mononeuritis multiplex) from symmetrical involvement of the peripheral nerves in polyarteritis nodosa. Miller thought that the symmetrical type of polyneuritis is common (1949). Heathfield and William (1954) described one case of mononeuritis multiplex and seven cases of symmetrical polyneuritis, and placed diabetic neuropathy first, infective polyneuritis second and polyarteritis nodosa neuropathy third in order of frequency.

Necropsy of cases of polyarteritis nodosa reveals macroscopic arterial lesions in the heart, kidney, liver and intestinal tract with yellowish mottlings (infarctions) due to arterial occlusion. Histology of peripheral nerves shows polyarteritis nodosa like lesions in vasa nervorum and nutrient vessels of the peripheral nerves with their occlusion and inflammatory oedema (Kernohan and Woltman, 1938; Miller, 1949; Lovshin and Kernohan, 1948; Heathfield and William, 1954).

In all such cases local pain, loss of tendon reflexes, subjective and objective sensory loss,

paresis, myositis tend to be conspicuous symptoms and signs. Particular reference may be made to the occurrence of unexplained foot drop, wrist drop in association with pyrexia, microcytic anaemia, albuminuria, raised E.S.R., increased gamma-globulin, altered liver functions, raised B.P., leucocytosis and wasting of muscles which are highly suggestive of polyarteritis nodosa.

Variety of neurological disorders are described in cases of polyarteritis nodosa: fits (Malamud and Foster, 1942), hemiparesis (Malamud and Foster, 1942), chorea (Neale and Whitfield, 1934), Parkinsonism (Sheinker, 1945), subarachnoid haemorrhage (Malamud and Foster, 1942), bulbar syndrome (Runge and Melzer, 1930), Ramsay and Hunt syndrome (Spiegel, 1936), clinical picture of intracranial neoplasm (Diaz-Rivera and Miller, 1946).

Symmetrical neuropathy in the legs was observed in two cases of polyarteritis and mononeuritis multiplex: right foot drop, wasting of the small muscles of the hands, asymmetrical loss of reflexes in the legs with subarachnoid haemorrhage, diplopia, 48 per cent. eosinophilia with asthma in one case; another case was suffering from asthma before the onset of neuropathy in the legs. One case, following meningococcal infection and sulpha drug therapy, developed mononeuritis multiplex: right Bell's, left ulnar and right external popliteal palsies which improved gradually. In two cases mononeuritis neuropathy (right external popliteal N. palsy) was associated with pyrexia, microcytic anaemia, raised E.S.R. and pain in legs. In one of them infective focus of staphylococcus was established, but appropriate chemotherapy was ineffective.

One case (female, aged 74) exhibited a mixed picture of polyarteritis and systemic lupus with symmetrical neuropathy in the legs. She was having recurrent attacks of conjunctivitis between 1951 and 1955, pleuritic pain with pulmonary rales at right base of the lung, off and on, jaundice, giddy turns and developed diabetes which was treated symptomatically. She developed coronary thrombosis on March 28, 1955, with congestive heart failure; now conjunctivitis recurred. She was treated by the anticoagulants, digoxin and mercurial diuretics. On April 23, 1955, she developed generalized measly and urticarial rash, angular stomatitis was noted on May 5, 1955; this was followed by glossitis, vitamin B and nicotinic acid was ineffective. Two weeks later she passed large offensive malaenous stools with abdominal colic. This was followed by dysphagia; skin lesions now were changed into healed polymorphic, purpuric and papulogranulomatous appearances; exfoliation was observed, later on, in the legs, peripheral arterial pulsations were absent in legs

with loss of deep reflexes; loss of sensation to pain, touch and vibration. Serum globulin and E.S.R. were raised. L.E. cells (lupus erythematosus cells) were absent from peripheral blood, and biopsy was negative. In view of above findings lupus-polyarteritis complex was considered and she was put on cortisone 100 mg. daily. Two weeks later a dramatic improvement was noted in her abdominal pain, dysphagia, diarrhoea and frequency of malaenous stools, which decreased gradually. Cortisone was decreased gradually and was stopped on July 26, 1955. She developed relapse of cardio-pulmonary symptoms four months later on; and cortisone was restarted. Now her neuropathy in the legs improved, but loss of deep reflexes persisted and skin was glassy in appearance. She became bald.

Three cases of drug sensitivity showed hyper-reflexia followed by areflexia, paraesthesiae in the legs, conjunctivitis, measles rash, abdominal pain and lymphadenopathy. Asymmetrical loss of reflexes was also observed in three cases (glandular fever, pulmonary lupus, hypersensitivity angiitis). Perivascular retinal exudate was observed in the case of hypersensitivity angiitis.

Aetiology.—Aetiology is still unknown. Further investigations are needed in the sphere of histochemistry and electron microscopy to throw more light on the pathogenesis of idiopathic necrotizing angiitides. Gruber (1925) suggested that it may be a manifestation of hyperergic reaction to variety of antigens: infections, toxic agents and drugs to which blood vessels had been previously exposed.

Ophüls (1923) expressed that individual types develop the disease and suggested that the lesions are the result of actions of various infections and toxic agents on the predisposed vessels. The observation that the disease often follows some infections, particularly streptococcal infection, and a similarity between it and acute rheumatism suggests that polyarteritis may be a result of allergy in a constitutionally defective individual. Association of asthma favours allergy as an aetiological factor.

Subsequently experimental production of hypersensitivity in animals revealed necrotizing lesions in the blood vessels (Klinge, 1929; Clark and Kaplan, 1937; Rich, 1942; Rich and Gregory, 1943). Such lesions and those produced by drug allergy differ to some extent from the classical type of periarteritis nodosa of Kussmaul and Maier (1866), and are termed hypersensitivity angiitis (Zeek, 1952-53; Knowles *et al.*, 1953).

Fibrinoid necrosis is also observed in non-specific injury: malignant hypertension, peptic ulcer, acute pancreatitis (Klemperer, 1948), overdose of DOCA and salt, large dose of ACTH

(Selye, 1944), and large doses of ergosterol diet rich in calcium and phosphorus (Ham, 1940).

Cortisone and ACTH opened a new field for the investigation of various types of necrotizing arterial lesions. Ehrenreich and Olmstead (1951) reviewed the detrimental and beneficial effect of these hormones in periarteritis nodosa. The variable effects of these hormones suggest more than one kind of necrotizing angiitis and need more clinical and experimental observations, whether one kind is benefited and other is harmed (Zeek, 1952). Polley (1956) of Mayo Clinic, home of cortisone, discussing the status of these hormones, described that overdose and chronic hormonal excess can produce mesenchymal reactions[†] simulating lupus, polyarteritis, light sensitivity, transfusion reaction, false serological reactions during blood grouping, articular pain and muscular ache. Edge, Fazlullah and Ward (1955) noted variable effect of cortisone in a case of hypersensitivity angiitis. There may be some types in the group of necrotizing angiitides, reacting differently to these hormones.

Recently Zeek (1952-53; Knowles *et al.*, 1953) suggested a new terminology, collectively, for various types of polyarteritis as necrotizing angiitides which is a non-committal as far as aetiology is concerned. They classified necrotizing angiitides into five clinical types. There may be other types still unclassified. The following is modified from Zeek classification:

1. Hypersensitivity angiitis.
2. Allergic granulomatous angiitis.
3. Polyarteritis: (a) Primary polyarteritis, (b) secondary polyarteritis.
4. Rheumatic arteritis: (a) Acute type, (b) chronic type.
5. Temporal arteritis.
6. Schönlein-Henoch allergic vasculitis.

Winkelman and Eckel (1932) described cerebral arteritis simulating the changes seen in acute disseminated lupus, in cases of rheumatism and chorea of moderate chronicity. Benda (1949) and Breutsch (1942) described cerebral arteritis with subintimal proliferation, filling lumen of small arteries, in cases of chronic rheumatism. Similar lesions are seen in the heart. These changes may

[†]In some cases these reactions are the manifestations of exacerbation of the disease process (polyarteritis or lupus) for which these hormones were used. Some years ago it was found that periarteritis nodosa lesions, produced by DOCA, can be duplicated by Pit. Somatotrophic hormone (H. Selye, 1951, *Lancet*, i, 483). This effect is inhibited by cortisone but only under conditions which induce marked adrenocortical atrophy. He also showed that cortisone prevents periarteritis nodosa in the mesenteric vessels, induced by DOCA, but does not exert such preventive action on the arteries of heart, kidney and certain organs.

reasonably be regarded as slow inactive sensitization of vascular tissue.

Before 1900 published cases of polyarteritis revealed macroscopic nodular lesions in every case; there was a microscopic confirmation. In 1903 Veszpremi and Jancso described a case of polyarteritis without macroscopic nodular lesions which was diagnosed microscopically (microscopic polyarteritis). In 1923 Ophüls was the first to describe the case of hypersensitivity angiitis, in which pulmonary small vessels were badly damaged, and there were widespread eosinophilic granulomatous lesions. Recently Edge, Fazlullah and Ward (1955) described a case of hypersensitivity angiitis in which pulmonary arteries were extensively involved.

Primary Polyarteritis Nodosa. This group of polyarteritis comprises the clinical type of polyarteritis described by Kussmaul and Maier (1866), characterized by a long course, remissions, exacerbations, nodular macroscopic lesions, polyneuritis, fever, anaemia and multi-systems involvement. Necropsy reveals nodular lesion at the point of branching of small and medium size arteries, widespread in distribution in the vessels of mesentery, pancreas, liver, kidney, coronary, peripheral vessels and absent from the pulmonary vessels unless pulmonary hypertension is associated. Splenic follicular arterioles are also involved. Arterial lesions of various ages are seen with the sequelae of renal hypertension and arterial obstruction.

Secondary Polyarteritis Nodosa. In this type of polyarteritis lesions in the arteries develop shortly before death in cases of severe renal disease and in hypertension or of both. In cases of malignant hypertension necrotizing lesions are seen in the kidneys, but inflammatory reactions are absent or minimal, while in the secondary polyarteritis there will be an inflammatory reaction (Knowles *et al.*, 1953). Recently Darmady *et al.* (1955) described a case of renal failure (tubular failure) due to polyarteritis in a woman of 31 years who had nephritis at the age of 12 and toxæmia of pregnancy at the age of 26, her necropsy revealing renal polyarteritis with interstitial inflammation.

Hypersensitivity Angiitis. This type of angiitis was first described by Ophül (1923), who emphasized the ten characteristic clinical features of the disease.

Previously described lesions of polyarteritis due to sensitivity to serum, sulpha drugs and other drugs: Dilantin (Rich, 1947), thiouracil (McCormick, 1950), iodine (Rich, 1947), differ to some extent from classical polyarteritis and are termed hypersensitivity angiitis (Zeek, 1952; Knowles *et al.*, 1953).

O'Brien and Story (1954) recorded a case of

hypersensitivity angiitis caused by phenylbutazone hypersensitivity. On necropsy histology, polyarteritis, granulomatous lesions and hypersensitivity angiitis were found.

Edge, Fazlullah and Ward (1955) described a case of hypersensitivity angiitis caused by penicillin, streptomycin, isoniazid and cortisone. Hypersensitivity angiitis is characterized by short fatal course, involvement of arterioles, venules, capillaries, interstitial inflammation in the involved viscera, and necrotizing glomerulonephritis. The lesions are of the same age with no healing stage on the microscopy. Vessels of kidney, heart, lungs and splenic follicular arterioles are specially involved. The arterial lesions are uncommon in the intestinal tract. Usually there is a history of sensitivity to serum, sulpha drugs and other drugs. There may be other types of hypersensitivity angiitis. Knowles *et al.* (1953) noted, in one of ten cases of hypersensitivity angiitis, early wire loop lesions of lupus in the renal tissues, in which course of the disease was delayed. Lupus disseminata and systemic lupus may be a form of hypersensitivity angiitis (visceral necrotizing angiitis). Recovery can occur in mild cases of hypersensitivity angiitis with exacerbation.

Allergic Granulomatous Angiitis. This type of angiitis is a systemic granulomatous condition and occasionally is described as a polyarteritis which eventually results after pulmonary eosinophilia and asthma with high eosinophilia, one to seven or many years later on.

Allergic angiitis was described by Churg and Strauss (1951), which is characterized by fever, asthma, eosinophilia, multinucleated giant cells granuloma in the extravascular tissues and serous membrane. The lesions are seen at various stages with eosinophilic exudates widespread in distribution, often in the lungs and spleen. The lesions are seen in any size of vessels with special affinity to small size arteries and veins. One of the presented cases was exhibiting recurrent onset of purpura without any cause, with transient jaundice, intermittent pyrexia, microcytic anaemia, raised E.S.R. and leucocytosis for two years; the sinus infection was established and drained; a course of appropriate antibiotics was given. He also used to get attacks of asthma off and on. Couple of months later he was seen with enlarged and tender liver in association with microcytic anaemia, leucocytosis pyrexia and raised E.S.R.; simulating subdiaphragmatic abscess. On laparotomy liver was enlarged and full of granulomatous lesions. Similar granulomas were found all over the peritoneum. Histology revealed multinucleated giant cells, granulomatous lesions around necrotic masses. In some cases giant cells

are arranged in radial fashion around necrotic eosinophilic masses or the small necrotic vessel.

Rheumatic arteritis. This type of arteritis is seen in acute fulminating rheumatism with carditis, involving the vessels of heart and lungs with Aschoff bodies and otherwise simulates hypersensitivity angitis. In the cases of chronic rheumatism lupus-like lesions are seen in the small cerebral vessels, first observed by Winkelman and Eckel (1932).

Temporal Arteritis. Horton *et al.* (1932) first recognized temporal arteritis. This is a benign member of the family with self-limiting course, characterized by pain over the temporal arteries with soreness, fever and malaise, pathologically subacute giant cell arteritis spreads longitudinally from vasa vasorum to the media along the vessels in contrast to the lesion in the polyarteritis nodosa with the sequel of thrombosis due to intimal hypertrophy. Similar lesions are found in the internal carotid arteries (Cloake, 1953), intracranial arteries, aorta, femoral, mesenteric, renal and coronary arteries (Cooke *et al.*, 1946). Ocular disorders, such as ptosis, diplopia, retinal exudates, papilloedema and loss of vision, which ultimately improves or is lost permanently in one-third of cases (Cooke *et al.*, 1946). Sometimes pain in the limbs is followed by impaired or loss of tendon reflexes, transient impairment of vibration, postural sense and cerebellar inco-ordination have been recorded (Cloake, 1953).

Schönlein-Henoch Allergic Vasculitis. Gairdner (1948) described that the Schönlein-Henoch syndrome, acute nephritis, rheumatic fever and polyarteritis, together form a family of disease linked by the tendency for one member to co-exist with the other. In one of his cases of this syndrome necrotizing arteritis was found in the brain. He regards intensive allergic vasculitis as the basis of the Schönlein-Henoch syndrome.

Allergic agent, usually, is a protein. The exciting factor may be found in the food (Squier and Madison, 1937), chocolate (Diamond, 1936), and tomatoes (Gairdner, 1948). Streptococcal infection, frequently, is incriminated.

Case.—A boy, 12 years old, with primary complex developed otitis media, which was treated by penicillin and sulpha drug. A week later he complained of abdominal colic, vomiting and diarrhoea, which continued for one week and followed by malaena. Three days later he passed a large offensive malaena. Hess test was negative and platelets were normal. Laparotomy revealed no evidence of surgical conditions except swollen and congested intestines. A week later he suddenly became unconscious with status epilepticus for four hours. Lumbar puncture revealed normal C.S.F. A week later diffuse purpura

was observed and now the diagnosis of Schönlein-Henoch syndrome was made. A week later he developed acute haemorrhagic nephritis with painful joints, fulfilling the criteria of the syndrome. He was treated symptomatically and by antihistamines. This is an example of allergic vasculitis, produced by the streptococcal allergy involving vessels of the intestine, brain, skin and kidneys.

It must be remembered that the site of allergic reactions to the antigen varies remarkably. In one case the same pathological process involves the arteries (polyarteritis) and in the other the capillaries (Schönlein-Henoch vasculitis); the latter should also be added to the group of necrotizing angitides. Thromboangiitis may be a form of slow reactive angitis.

(b) *Allergic Polyradiculoneuritis (Landry-Guillain-Barré Syndrome)*

This syndrome is described under various titles. None is self-explanatory. Although this is called an infective polyneuritis, infective agents have never been isolated. In the present state of knowledge it is reasonable to call it 'allergic polyradiculoneuritis' until definite aetiology is known. Attention has been drawn that 50 per cent. of the cases manifest the disease two to three weeks after the non-specific upper respiratory tract infection or gastro-intestinal infection at a time when antibodies are formed and its association with post-vaccinal, post-exanthematous and drugs hypersensitivity illnesses, also, with polyarteritis (Liversedge and Leather, 1953) and rheumatoid arthritis (Grant and Leopold, 1954) suggests hyperergic manifestation to these noxious agents. Recently this is supported by the experimental production of an identical disease in rabbits by intradermal injection of rabbit sciatic nerve or spinal ganglia with heat-killed tubercle bacilli, as an adjuvant, and this disease was associated with high protein in the C.S.F. without pleocytosis (Waksman and Adams, 1955). This allergic experimental polyneuritis of Waksman and Adams has made a momentous advancement in our knowledge about diseases of the peripheral nervous system of unknown origin, and also shows that there are different kinds of the antigens in the peripheral and central nervous system; the former produce allergic polyneuritis and the latter allergic encephalomyelitis in the experimental animals.

Guillain *et al.* (1916) emphasized raised protein without pleocytosis in the C.S.F. of patients suffering from this disease, as the diagnostic feature of the disease. Sometimes, in the early stage of the disease, C.S.F. is normal and proteins increase gradually as the disease progresses. The

amount of proteins depends upon the obstruction of exit of the C.S.F. due to oedema, congestion of the roots, as they pass through the inter-vertebral canals, and increased vascular permeability (Haymaker and Kernohan, 1949). Roots entry zones are frequently involved and these are bathed freely in the C.S.F. Aring (1945) described changes in the C.S.F. proteins collected at various levels: L₁ vertebral: 330 mg. per 100 ml.; cisternal level: 14 mg. per 100 ml. L₂ vertebral: 380 mg. per 100 ml.; cisternal level: 88 mg. per 100 ml. L₃ vertebral: 1,400 mg. per 100 ml.; cisternal level: 182 mg. per 100 ml.

Spinal block has been shown by intrathecal-thorotrast. Pleocytosis in the C.S.F. is noted when meninges are involved. Recently Fazlullah (1956) reported a case of Landry-Guillain-Barré syndrome with extensive flaccid motor paralysis, peripheral sensory neuropathy and pleocytosis—80 cells per c.mm. with evidence of meningeal involvement. Haymaker and Kernohan (1949) described pleocytosis up to 514 per c.mm., and ascribed pleocytosis to meningeal involvement. Waksman and Adams (1955) also observed pleocytosis in their allergic experimental polyneuritis in case of meningeal lesions.

There is no complete agreement about the pathology of this disease. In some fatal cases no definite pathological changes have been found. In some cases degeneration of myelin sheath with perivenous infiltration of plasma cells, lymphocytes and mononuclear cells in the spinal ganglia, roots, and peripheral nerves has been observed. In mild cases myelin degeneration is limited to a few segments with sparing of axis cylinder, while in severe cases whole sensory neurone is damaged. Notable feature of the disease is perivascular or perivenous inflammatory cells infiltration in the peripheral nerves which is similar to the reaction of delayed tuberculin sensitivity and other allergic states. Similar perivascular cellular infiltration is seen in the heart, lungs, liver, kidneys and suprarenals.

Variable clinical picture and course suggest that a single disease entity manifests under the guise of several slightly different clinical syndromes. Recently Adams (1955) classified this idiopathic polyneuritis into the following clinical types:—

1. Syndrome of symmetrical ascending motor paralysis with minimal sensory change.
2. Syndrome of ophthalmoplegia, fascial diplegia, bulbar palsy and descending motor paralysis of the trunk and limbs.
3. Glandular fever syndrome with ascending motor and sensory paralysis.
4. Asymmetrical sensorimotor spinal-cranial polyneuritis of subacute onset.

Sometimes a combination of one of these has been observed. Recently Fazlullah (1956) reported three cases of Landry-Guillain-Barré syndrome, fulfilling the criteria of the above-mentioned type 4. One of the presented cases exhibited glandular fever syndrome with asymmetrical neuropathy, simulating, partly, type 3 syndrome.

Case.—A female, aged 34, following sore throat, two weeks later, developed generalized erythema, itching, oedema of face and limbs with paraesthesiae. This was followed by jaundice, cervical lymphadenopathy, splenic enlargement, polyarthritis, conjunctivitis, intermittent pyrexia and tachycardia. Asymmetrical loss of deep reflexes with loss of sensation to pain, touch and vibration were noted in the legs. C.S.F. was normal. Paul Bunnell test was repeatedly negative. Abnormal lymphocytes were found in the peripheral blood. L.E. cells were absent from the peripheral blood. Muscle and gland biopsy was negative for polyarteritis. Serum globulin was normal. Her condition was deteriorating on symptomatic treatment, and she developed severe exfoliative dermatitis with haemorrhagic tendency in the hands, conjunctivitis, persisting obstructive type of jaundice, angular stomatitis and glossitis. She also complained of pain in the right hypochondrium, and liver was palpable and tender. She was put on cortisone 100 mg. daily two weeks after the onset of the present illness. Dramatic improvement was noted in her clinical condition. Cortisone was reduced gradually as her clinical condition improved without any evidence of relapse. Two months after discontinuation of cortisone, she developed relapse of her previous symptoms: generalized itching, erythema and fascial oedema, which were controlled by antihistamines. Her eosinophilia count was 2,000.

Recently Towers (1955) reported two cases of similar glandular fever syndrome due to PAS sensitivity. One of his cases developed Guillain-Barré type of polyneuritis with raised C.S.F. protein without pleocytosis. Barnes and Barnes (1955) suggested that the drug containing primary aromatic amines like PAS can produce glandular fever syndrome.

Glandular fever syndrome with neuropathy, following non-specific upper respiratory infection and drug sensitivity, favours an allergic reaction to these noxious agents and throws light on the pathogenesis of the so-called glandular fever. Though infective aetiology is suggested, no infective agent is confirmed. Evans (1947), in human beings, had negative results as regards transmission of the disease. Dramatic response to cortisone, in the above case, with evidence of tuberculin type of sensitivity and production of an identical

syndrome by drug sensitivity, support an allergic mechanism. Further clinical and experimental evidences are needed to evaluate this problem.

Conclusions

In hypersensitivity states the neurological disorders are ischaemic in origin, probably due to primary vascular insult, allergic oedema and disturbed neuronal biochemistry resulted by the immunological process, otherwise we cannot comprehend the pathological findings, clinical sequence of non-specific infection followed by neurological disorders after an interval of two to three weeks, at a time when antibodies are formed and prompt recovery by ACTH or cortisone.

It is a high probability that there are many antibodies having an affinity to injure different tissues such as vessels, myelin, kidney, myocardium and mesenchymal tissues alternatively, autoimmunization with multiple autoantibodies seems as good as any at the moment. We know little about the cell-fixed antibodies and other antitissues antibodies.

In the allergic disorders of the central and peripheral nervous system the earliest pathological changes are perivascular cellular infiltration and oedema, amelioration of which gives rise to complete regression of neurological disorders, but if the reaction to the certain allergens is very violent then this reaction will follow with necrotizing vascular lesions with severe neuronal damage.

The disease process may produce different clinical syndromes by attacking in one case arteries (polyarteritis), in another capillaries (Schönlein-Henoch vasculitis), in other veins and perivenous neurone (allergic encephalomyelitis of Lumsden, post-exanthematous and spontaneous disseminated encephalomyelitis), and in another peripheral nerves, spinal roots and ganglia (allergic experimental polyneuritis of Waksman and Adams or Landry-Guillain-Barré syndrome). There may be two kinds of antigenic processes, one attacking the peripheral neurone and the other central neurone of the central nervous system which is supported by the experiments of Waksman and Adams (1955) and Lumsden (1948), or both may co-exist. Eventually these syndromes will emerge as variants of a single disease process and it is possible that a common aetiology may be established.

Persistent low-grade infection induces delayed type of hypersensitivity with cell-fixed antibodies, eventually produces necrotizing inflammation which commonly occurs in the diseases of collagen (Long, 1956). If bacteria persist in the body, immunity to toxins and hypersensitivity to allergens are associated phenomena; at this stage administration of cortisone and ACTH depresses

the sensitivity to bacterial allergens (Long, 1954, 1955, 1956). These hormones probably reverse the destructive enzymatic processes in the affected cells rather than the unknown cause or suppressing the antibodies formation, since cortisone acts more rapidly than an effect on the antibodies would be expected and the equal prompt recurrence of the illness after its discontinuance. §

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Continued on page 144

§Selye (1951) contends that the pathogenic basis of collagenous disorders may be a disturbance in the ratio of minerals and glucocorticoids, ACTH and cortisone on the one hand, pit. somatotrophic hormone and DOCA on the other hand, exert diametrically opposed effect and cardiovascular-renal lesions, caused by the pit. somatotrophic hormones, are aggravated by simultaneous administration of cortisone. This fails to do so in the adrenalectomized rats.

Investigations, on steroids in the urine of patients with rheumatoid arthritis, show no evidence of adrenal insufficiency. It has been postulated that a relative adrenal insufficiency is produced due to an increased hormone demand in tissues involved in this disease. In such cases ant. pit. stimulus, although increased, would not result in an increased plasma level of the hormones. In cases of rheumatic fever high plasma ACTH and low cortisone has been reported (V. C. Kelly, 1955, *Ann. N.Y. Acad. Sci.*, **61**, 369). This might be due to adrenal exhaustion, possibly as a result of increased steroids demand in the tissues.

In cases of rheumatoid arthritis, low plasma corticoids (J. E. Warren, 1956, *Ann. rheum. Dis.*, **15**, 70) and decreased urinary steroids excretion (S. R. Hill, Jr., H. L. Holley, W. R. Starnes, and L. L. Hibbett, 1956, *Ann. rheum. Dis.*, **15**, 69) in the early morning can be correlated with the early morning exacerbation of muscular stiffness. This might reflect a change in the hypothalamus-pituitary-adrenal axis.

Recently abnormal steroid metabolites have been isolated from urine of cases with rheumatoid arthritis which disappear after ACTH administration (H. Wilson, 1956, *Ann. rheum. Dis.*, **15**, 70). Patients with post-partum pit. necrosis are unduly liable to develop rheumatism in knee (H. L. Sheehan, 1939, *Quart. J. Med.*, **8**, 277). The changes in the cellular structure of rheumatoid and lupus hypophysis consist of degranulation of mucoid cells (A. G. E. Pearse, 1950, *Lancet*, **i**, 954). There is an increasing evidence that ant. pit. may be implicated in the aetiology of collagenous disorders. It seems that there may be some quantitative or qualitative abnormality in the endogenous corticotrophin. However, there is no increased incidence of rheumatoid arthritis in cases of Addison's disease or in chromophobe adenoma with pit. insufficiency. It is impossible, at present, to ascertain whether this alteration in the hypothalamus-pituitary-adrenal mechanism is a cause or the result of chronic disease state. Further clinical and biochemical investigations are needed to confirm the role of 'hormonal imbalance' in the pathogenesis of collagenous diseases.

It would appear from the above that the reflex is indeed abolished when some of the more potent anaesthetics such as ether are used. Unfortunately, these have usually some other disadvantages, such as toxicity or inflammability, and at the present time with the widespread use of the diathermy, etc., they are usually contraindicated. The fact that less potent agents and combinations such as gas, Pethidine and light Trilene do not greatly depress the reflex was well demonstrated in this case. That this is of little consequence, however, is equally clear since it is comparatively simple to nullify the effects of the reflex by employing drugs with vagolytic and sympathomimetic properties. The agents of choice would seem to be Atropine and Nor-adrenaline.

Suggested Scheme of Treatment

1. Preliminary assessment of state of collateral cerebral circulation by electroencephalogram and crossed carotid angiogram.
2. Exploration of tumour through a long incision along the anterior border of sterno-mastoid to give a wide exposure.
3. If possible to remove the tumour without jeopardizing the internal and common carotid vessels, do so.
4. If not, apply a temporary ligature to the common carotid, partially occluding it, and biopsy the tumour.
5. If the biopsy shows the tumour to be malignant, or if the symptoms warrant it, re-

explore three weeks later and excise the tumour together with the bifurcation of the carotid.

6. If possible, insert an arterial graft, but if not anastomose the distal cut ends of the internal and external carotids.

7. Carry out a stellate ganglion block with local anaesthetic.

8. Give anticoagulants post-operatively.

9. Nurse in head-down position in an oxygen tent for several days.

Summary

A case of carotid body tumour with marked sinus syncope is described.

The problem of treatment of these tumours is discussed and a plan of treatment is given.

The effects of various drugs on the syncopal attacks are discussed.

Our thanks are due to Dr. R. R. Hughes, under whose care the patient was admitted, and to Mr. J. Cosbie Ross, who performed the operation, for permission to publish this case.

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