

(From the Newbury District Hospital Allergy Clinic)

MANIFESTATIONS OF ALLERGY IN THE CENTRAL NERVOUS SYSTEM

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In the past twenty-five years so many new journals have appeared and so many papers have been published claiming allergy as the cause of such a variety of human ills that one is reminded of the mass of publications in the previous quarter century claiming syphilis as a possible cause of every pathological state and left wondering whether allergy is just one more of the great imitators of medicine, i.e. whether there is a true asthmatic state and a pseudo one due to allergy, a true epileptic state and a pseudo one, a true sinusitis and a pseudo one. It will not be possible to assess the value of this idea until some method of reproducing the signs and symptoms of the allergic attack has been standardised, with a test able to be applied by all trained personnel in any hospital clinic or consulting room. This paper describes such a test in its simplest form, with details of results in its special application to manifestations of allergy in the nervous system, as typified by attacks of migraine, Ménière, epilepsy, and disseminated sclerosis.

In 1910 Barger and Dale demonstrated the presence of histamine in ergot and reported some of its pharmacological properties; since then, for forty years, physiologists and clinicians have tried to find the secret of its significance in our biological make-up. Some teams of workers have regarded

histamine, though present in all tissues, as detrimental to human well-being if concentrated in one tissue or body-space in abnormal quantities, and so have developed a new attitude to treatment of allergic conditions, with the application of anti-histamine drugs; while others have tried to harness histamine itself for its therapeutic value in small doses. Perhaps the greatest stumbling block to any advance in this field has been the assumption that a close analogy existed, pharmacologically, between laboratory animals and man, although fifteen years ago Ratner (1939) showed that whereas animal tissues continue to react in a predictable manner to successive doses, human tissues may be hyposensitised by repeated treatments with small doses of histamine. (For discussion of this subject, see Selle (1946).

Histamine was used therapeutically as long ago as 1921 by Mr. Frank Coke, of London, for the treatment of migraine: since that date its use has been tried by many workers in many hospitals both for the accepted allergic conditions as asthma, hay-fever, urticaria and migraine, and for some rather more doubtful manifestations as rheumatoid arthritis, gout, epilepsy and disseminated sclerosis. Perhaps the variations in results are due to our ignorance not of "what to use" but rather of "how to use it". There seems no doubt now that histamine by injection or by ionophoresis is the treatment of choice for migraine, as handled by Horton and his colleagues at the Mayo Clinic; for urticaria, especially if the attention to detail as described by Prince and Etter is appreciated; and for keratitis rosacea and allergic iritis where the main object is to prevent further deterioration in an already damaged cornea or iris (Walker, 1948).

While use was being made of the method of Prince and Etter in giving histamine by electrophoresis for the treatment of allergic skin conditions, especially those involving the skin of the face and eyelids and eventually the conjunctivae, both palpebral and bulbar, the diagnostic significance of this method became apparent. It was realised that although all human beings can be made to "flush" with histamine, only those with

TABLE I

Clinical diagnosis	No. of patients	Diagnosis confirmed by histamine	%	Symptoms produced. (Severity depending on dose and time)
Migraine	280	252	90	Hemiheadaches c nausea or c visual upsets
Ménière	25	23	90	Giddiness Falling to side Occasional deafness
Epilepsy	20	14	70	Tonic spasm. Rapid pulse. Dilated pupils (14) Status epilepticus for several hours (2)
Disseminated Sclerosis .	75	42	56	Diplopia (18) Nystagmus (22) Pain in cervical spine region (38) Vertigo & deafness (2)

some allergic manifestation of hypersensitivity produce other symptoms at a distance from the electrodes. In patients with asthma, urticaria or hay-fever, either present or potentially present, the histamine "flush" was followed by a spasmodic wheeze, a wheeling or an acute attack of rhino-conjunctivitis respectively. Typical hemi-headaches, with or without visual disturbances, vomiting, etc., were produced in migraine patients, and an obvious labyrinthine giddiness resulted in the Ménière victims. The method is especially useful in the diagnosis of allergy as the main etiology of the many syndromes ranging between true migraine and true epilepsy.

EXPERIMENTAL DETAILS

Two c.c.s. of a 1 % solution of Histamine-acid-phosphate in distilled water was applied to a pad of 6 layers of tissue

paper and placed on the right forearm under the positive electrode of a small battery unit, the negative contact being made by 5 c.c.s. saline on a similar pad on the left arm. A 4.5 volt dry battery was arranged in circuit to give a gradually increasing current up to 3 milliamps for adults, (2 milliamps for children under 10, and 1 milliamp for infants up to 3 years). The treatment was continued for 10 minutes unless acute symptoms developed in a shorter time.

Tables II to V show comparative results on allergic and non-allergic patients of same sex, age group and social environment.

TABLE II
Migraine.

A.	B.
V.P. male (46).	S.N. male (39).
Severe migraine for 15 yrs: often off work 3 days/week.	Headache with vomiting 2 or 3 times a week for 8 years.
Histamine gave flush and severe pain over right eye in 8 mins, Nausea in 10 minutes.	Histamine gave flush in 9 minutes but no headache even after 15 minutes.
Intradermal tests	
Fish ++	Wheat +
Milk +++	Barley +
Egg ++	
Avoided these foods for 6 weeks and had only one headache.	Avoiding these foods did not help.

Migraine.

DISCUSSION

Though many writers have attempted to draw a dividing line between migraine and histamine headache, it seems clear from Table I that the distinction is one of degree only. Ninety percent of 280 cases of migraine do reproduce their own peculiar type of symptoms if given the right amount of histamine at the correct rate for the correct time: and, perhaps more important still, they do not produce symptoms due to histamine dysfunction in other parts of the brain or spinal

TABLE III
Menière.

A.	B.
H.W.B. female (35). Menière attacks once every two or three weeks for 10 years.	F.F. female (32). Vertigo with pain in head and falling to left about once a week for 5 years.
Histamine gave general flush in 8 minutes followed by swaying feeling and right sided pain in head in 10 minutes.	H. produced flush but no vertigo and no pain.
After 6 similar doses of histamine in Nov-Dec 1951, this patient has not had any more attacks.	(Some improvement on oestrin treatment.)

TABLE IV
Epilepsy.

M.P. female (10). Epilepsy, minor and major, since age 2.	H.B. female (8). Epilepsy, minor all her life. Two major attacks recently.
Histamine produced arched back, extended legs, rapid pulse & dilated pupils in 6 minutes so treatment stopped.	Histamine gave flush but no other symptoms.
Allergy tests: Fish +++ Blackberry +++ Primulas ++	Allergy tests: Nil found.
While avoiding these foods for 6 months has not needed drugs & has been free from attacks.	

cord. The shock tissue appears to be a very sharply defined portion of the sensory system. Possibly the other ten percent could also reproduce their attacks if one knew more of the necessary conditions, though, more probably, their so-called migraine was really part of a more complicated syndrome with a very different pathology.

TABLE V
Disseminated Sclerosis.

A.	B.
M.N. female (45).	R.B. female (36).
Diagnosed as D.S. when aged 24. Had many types of treatment but legs getting more spastic during test 2 years (since starting ox-liver inj.)	Diagnosed as D.S. when aged 33. Rt. leg spastic and left optic atrophy.
Histamine gave flush in 7 minutes, pain in cervical spine area in 9 minutes and diplopia in 10 minutes.	Flush but no other symptoms.
Tests Horsehair ++	Fish +
Feathers +++	
Dog-hair +++	Died 6 months later with cerebral tumour.
Beef +++	

Menière's Disease.

Whether one is justified in including menière's syndrome in a dissertation on the C.N.S. now seems doubtful, for the simplest possible pathology necessary to explain the symptoms of 23 out of 25 cases in Table I is a collection of fluid in the middle or inner ear due to the action of histamine on a very localised tissue. Perhaps the 25 cases are too few to draw conclusions, but it does seem essential that all patients with recurrent vertigo and deafness should be investigated by a competent allergist.

Epilepsy.

At the meeting of the I.A.A. in Zürich in 1951 Davidson (U.S.A.) presented a summary of answers to a questionnaire sent to allergists in the U.S.A. on the subject of "Allergy and Epilepsy". Since then many allergists have been asked to investigate epilepsy, especially in childhood with a hope of finding some allergic origin for this cause of social ostracism. The 20 cases included in Table I were all under the age of 25 and were all partly or completely controlled by drugs. 14

of the 20, i.e. 70 % reproduced their symptoms with a mild dose of histamine, and did not get symptoms of migraine, or of asthma, or of any other manifestation of allergy. The same 14 have been able to give up their drugs when avoiding certain inhalents or foods to which they were found to be allergic on intradermal tests, so hope has been established in the minds of many parents and potential parents who themselves have suffered from epilepsy.

One is often told that a patient's "fits" began after a motor accident, a fall from a tree, or after other trauma: surely these unfortunate happenings are probably only the cause of localising the shock tissue in the motor cortex, rather than in the lungs, or on the skin of the particular patient.

Disseminated sclerosis.

The results published by Jonez from his clinic in Tacoma, U.S.A. have been a challenge to the medical world for renewed efforts to conquer this dire condition. That Jonez has discovered part of the truth there can be no doubt: but from the investigation and later treatment of the 75 cases included in Table I it seems equally true that while some patients respond remarkably well to any and all anti-allergic treatments many others do not. All 75 patients had been given a verdict of "disseminated sclerosis" by reputed neurosurgeons of Great Britain: there seems no clinical difference between those who should be classified as "true disseminated sclerosis" and those "pseudo" ones which are an allergic manifestation of the real condition. It, therefore, becomes necessary for all D.S. patients to be tested for allergy by some method. and, at the present time, the histamine method seems the most satisfactory.

SUMMARY

- (1) The use of histamine-acid-phosphate by electrophoresis as a diagnostic test for allergy is described, and its application to 400 patients with possibly allergic manifestations in the central nervous system summarised.

- (2) It is concluded that whereas 90 % of all migraine and Menière conditions are allergic, only about 50 % of those diagnosed clinically as epilepsy or as disseminated sclerosis are true allergy.
- (3) The suggestion is made that there is a true epilepsy and a pseudo one due to allergy, a true disseminated sclerosis and a pseudo allergic one.

ZUSAMMENFASSUNG

- (1) Die Verwendung von saurem Histamin Phosphat mittels Electro-phorese als diagnostische Probe für Allergie wird beschrieben, und deren Anwendung bei 400 Patienten mit möglicherweise allergischen Erscheinungen im Zentral Nerversystem wird zusammenfassend behandelt.
- (2) Es wird gefolgert, dass, während 90 % aller Migräne und Ménière Zustände allergisch sind, nur ungefähr 50 % der klinisch als Epilepsie oder als multiple Sklerose diagnostizierten Zustände echte Allergie sind.
- (3) Es wird vorgeschlagen dass man eine echte Epilepsie und eine durch Allergie verursachte Pseudo-Epilepsie unterscheiden soll, ferner eine echte disseminierte Sklerose und eine allergische Pseudo-Sklerose.

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