VALUE OF HISTAMINE SKIN TESTS IN MÉNIÈRE'S DISEASE

BY

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In 1861 Prosper Ménière (1861a, 1861b) described the disease that bears his name. Little has since been added to his description of apoplectic attacks of vertigo occurring in association with tinnitus and variable but progressive deafness. He suggested that the condition arose in a previously healthy ear, and that the semicircular canals were the site of the functional disturbances. Seventy-seven years later the careful histological studies of Hallpike and Cairns (1938) proved that he had been correct. They demonstrated a gross dilatation of the endolymphatic system, with degenerative changes in the organ of Corti, and an absence of the normal connective tissue around the saccus endolymphaticus. There was no evidence of inflammation or haemorrhage. The pattern of the disease is thus clear and its pathology demonstrated, but the cause of the disturbance in the inner ear is still undetermined. As might be expected, there are many theories, each supported by corresponding methods of treatment. Strangely enough, these treatments are all attended by much the same degree of success (Atkinson, 1945a).

Mygind (1924) and Dederding (1929) suggested a retention of water in the body, of which the disturbance in the labyrinthine and cochlear systems is but a part. Furstenberg *et al.* (1934) believed that there was a retention of sodium chloride rather than of water, while Wright (1937, 1946) maintained that focal infection was the cause of the disease. Crowe (1938) found it difficult to believe that there was some generalized disturbance, because Ménière's disease was so often, at least initially, unilateral, and he concluded that pressure changes in the endolymph were responsible. Eustachian obstruction, labyrinthine haemorrhage, aberrant vessels, and vascular spasm have all had their advocates. Latterly it has been suggested that Ménière's disease is an allergic response and that histamine may be used in its diagnosis and treatment. It is with this theory that this paper is concerned.

Allergy and Histamine Sensitivity

Although a great deal of discussion has been devoted to the conception that Ménière's disease is due to allergy, there is no direct evidence of this. The disease is not familial, it tends to occur in middle life, and other allergic manifestations are not often found associated with it. The indirect evidence may be stated as follows: the pathological process is one of a non-inflammatory extracellular oedema. The symptoms, both cochlear and vestibular, are fluctuant. Often the deafness and tinnitus increase during an attack of vertigo, to improve in the interval. The ultimate course of the disease is variable, too. Some cases have attacks at intervals of months or years, suffering little diminution in hearing; in others the disease is steadily progressive until, finally, complete deafness and an insensitive labyrinth result in a cure of the vertigo. This variability has been put forward in favour of a reversible mechanism that might well be allergic. But only a few actual instances of

antigen-antibody type of allergy have been recorded. For this reason Williams (1944, 1947) suggested that some form of physical or intrinsic allergy existed. By this he meant the type first postulated by Duke (1925) in which there is no antigen-antibody reaction, but instead a sensitivity to heat, cold, atmospheric pressure, or to endocrine or emotional factors.

Atkinson (1941, 1943a, 1943b) approached the subject from a different angle. He suggested that Ménière's disease was a "syndrome that can be produced by at least two causes." It was a vasomotor disturbance which in one group of cases was allergic in origin and in the other was due to vasospasm. But he was able to demonstrate hypersensitivity in only two of his cases in the allergic group. He argued that, as it was well known that the final results of allergy in the tissues were due to the liberation of a histamine-like substance, then increased sensitivity to intradermally injected histamine should be a general indication of the presence of allergy. This supposition was based on the work of Dzsinič and Gallé (1939), who had used injections of histamine as an intradermal test in cases of asthma. These authors stated that it was possible to desensitize the tissues to histamine by graded injections of that substance. Sheldon and Horton (1940) treated 11 cases of Ménière's disease during the acute attack of vertigo with intravenous histamine and reported dramatic results. This, however, was not surprising, as it is known that the attack of acute vertigo resolves without treatment. Atkinson (1941) adapted the test of Dzsinič and Gallé, using an intradermal injection of 0.01 mg. of histamine dihydrochloride in 0.1 ml. of saline. His patients fell into two groups—histamine sensitive (20%) and histamine insensitive (80%)—as a result of the test. A positive reaction showed a wide area of erythema, $1\frac{1}{2}$ to 2 in. (3.8 to 5 cm.) in diameter, a large weal of $\frac{1}{2}$ to $\frac{3}{4}$ in. (1.25 to 1.9 cm.) diameter, and long trailing pseudopodia, 1 in. (2.5 cm.) or more long, which appeared in three to five minutes, fading after 20 minutes but still present at the end of 30 minutes. Small buds at the edge of the main weal were not taken as positive. In the normal person—that is to say, the histamine-insensitive group—the erythematous flare was $1\frac{1}{4}$ to $1\frac{1}{2}$ in. (3.1 to 3.8 cm.) broad, and the weal $\frac{1}{4}$ to $\frac{1}{2}$ in. (0.8 to 1.25 cm.), both fading somewhat more rapidly than did the positive response. The cases that were found sensitive all responded well to desensitization with histamine. In those patients who did not give a positive skin reaction, Atkinson argued, the symptoms were due to vasospasm. These he treated with nicotinic acid, a vasodilator. Both mechanisms he thought could lead to increased endolymph production in the labyrinth.

Williams (1944) criticized this theory on the ground that he got equally good results in both groups with nicotinic acid, while Rainey (1943, 1945) and Lillie *et al.* (1944), disregarding any form of skin-testing, got good results with histamine only. Farmer (1945) was quite unable to agree that allergic individuals were more sensitive to histamine than normal persons, and concluded that the test was valueless in this respect. But this criticism had already been anticipated by Atkinson (1943b), who withdrew the statement that the test was a true indicator of allergy, but insisted that its results were valid in dividing patients with Ménière's disease into two groups. Atkinson (1945b) then gave more details of his test, and emphasized that it was valid only if one adhered strictly to his method. Further, it was now his

opinion that the size of the flare was of secondary consideration and that the true criterion of a positive result was the presence of pseudopodia.

A year later Atkinson (1946a, 1946b) again modified the test. He now uses 0.05 ml. of a 1/10,000 solution of histamine base—that is to say, 0.005 mg. of base in 0.05 ml.—which must be injected into the volar surface of the forearm, 2 in. (5 cm.) below the elbow. The normal response is now stated to be a flare of 1 to 1½ in. (2.5 to 3.8 cm.) diameter and a weal of ¼ to ½ in. (0.6 to 0.8 cm.). In the histamine-sensitive the flare is 2 to 2½ in. (5 to 6.3 cm.) and the weal ¾ to 1 in. (1.9 to 2.5 cm.). Pseudopodia are an essential indicator of sensitivity—sometimes a long trailing one of 1 to 2 in. (2.5 to 5 cm.) length, and sometimes two or more shorter ones. Small buds are not to be considered positive. His work has recently been confirmed in this country by Kodicek *et al.* (1950). The theory and corresponding method of treatment are based on the assumption that in a proportion of patients with Ménière's disease there exists a state of abnormal sensitivity to histamine which can be recognized by an abnormal skin response. Yet no one seems to have published figures of the skin responses of normal persons by this method. I have attempted to do this.

Investigations

Intradermal skin tests were performed on 50 cases of Ménière's disease. There were 35 men and 15 women, and the average age of the whole series was 47 years. In spite of what has been said about the association of the disease with allergy, only two patients suffered from migraine, and one had true asthmatic attacks. None gave a history of urticaria, angioneurotic oedema, hay-fever, or any food sensitivity in relation to the vertigo.

Similar tests were carried out on 50 controls—33 men and 17 women—the average age being 39 years. Twenty-three of these were in normal health, either students or out-patients with no organic disease, and 27 were patients from the medical wards. The only criterion adopted in the selection of either group of controls was that they should not suffer from any allergic disease or migraine.

Methods

Two solutions were used: (A) 0.01 mg. of histamine dihydrochloride in 0.1 ml. of normal saline (equivalent to 1/20,000 histamine base). (B) 0.005 mg. of histamine base in 0.05 ml. of normal saline (equivalent to 1/10,000 histamine base).

These are the first and second solutions advocated by Atkinson. As 1 mg. of histamine dihydrochloride contains 0.57 mg. of histamine base, it can be seen that the absolute quantity of histamine in each solution is almost the same, but B is twice the concentration of A.

Intradermal injections were made on the volar surface of both arms in the region of the elbow. A tuberculin syringe was used, graduated to 0.01 ml. Three sites on each arm were chosen—one just above and two

just below the elbow crease. Both solutions A and B were used, being distributed as shown in Fig. 1. The characteristic raised white weal and surrounding red flare developed in every case, and sometimes one or more raised red lines were seen to radiate out from the weal—the so-called pseudopodia (see Fig. 2). After five to ten minutes the appearance had developed to its maximum and the outline was inked on to the skin. A

FIG. 2.—Typical examples of skin responses. Half natural size.

piece of "cellophane" paper was then placed over the area and a tracing taken. This was kept as a permanent record and measured. As to the method of measurement, I tried both a planimeter and direct computation from squared graph paper. These are excessively tedious, and are hardly more accurate than the much simpler method of taking the average of two diameters at right angles. I have given the diameters of flare and weal in inches, as this makes comparison with Atkinson's work easier.

Interpretation of Results

The Pseudopodic Processes

1. Atkinson's later and stricter criterion of a positive response is defined as a weal produced by histamine solution B that shows one or more pseudopodia of 1 in. (2.5 cm.) or over in length, at a site 2 in. (5 cm.) below the bend of the elbow (3B and 6B in Fig. 1). Five of the cases of Ménière's disease and eight of the controls were positive.

2. With the above criterion, but including also Atkinson's earlier testing solution A, four sites are available below the elbow (2A, 3B, 5A, and 6B in Fig. 1). Seven of the cases of Ménière's disease and eight of the controls were positive.

3. Again considering as positive a pseudopodium of 1 in. (2.5 cm.) or more in length, with either solution A or B, and including a further site 2 in. (5 cm.) above the bend of the elbow on either side (1B, 2A, 3B, 4A, 5A, and 6B in Fig. 1), 12 cases of Ménière's disease and 13 of the controls were found positive.

4. Lastly, as others (Williams, 1944; Farmer, 1945) have taken 1 cm. as the measure of the pseudopodium in judging a positive reaction, I have counted the number of cases, using all six sites and both solutions, that would have to be called positive. By this method 37 of the cases of Ménière's disease and 32 of the controls were positive.

Clearly, whichever dilution of histamine, whichever site, and whichever length of pseudopodium is chosen,

FIG. 1.—Sites used for the injection of solutions of A and B.

there is no significant difference between the 50 cases of Ménière's disease and the 50 controls. The results are summarized in Table I.

TABLE I.—*The Production of Pseudopodia from a Histamine Weal in 50 Cases of Ménière's Disease and 50 Controls*

Criteria of a Positive Response	No. of Cases	
	Ménière	Controls
1. 1 in. (2.5 cm.) or more long with solution B (sites 3B and 6B)	5	8
2. 1 in. (2.5 cm.) or more long with solutions A and B (sites 2A, 3B, 5A, 6B)	7	8
3. 1 in. (2.5 cm.) or more long with solutions A and B (sites 1B, 2A, 3B, 4A, 5A, 6B)	12	13
4. 1 cm. or more long with solutions A and B (sites 1B, 2A, 3B, 4A, 5A, 6B)	37	32

Finally, it has been observed that the greater the number of tests performed the more likely is it that a pseudopodic process will appear. This is shown in Fig. 3.

Fig. 3.—Chart showing how the number of cases developing pseudopodia increases with the number of tests performed.

The Weal and Flare

Although Atkinson has now stated that the presence of pseudopodia is more important than the size of the triple response, he still gives measurements of what he believes to be abnormal. The weal in the normal is 0.25 to 0.3 in. (6.4 to 7.6 mm.) and the flare 1 to 1.5 in. (2.5 to 3.8 cm.) diameter. In the histamine-sensitive subject they are 0.75 to 1 in. (1.9 to 2.5 cm.) and 2 to 2.5 in. (5 to 6.3 cm.) respectively. My findings in the 50 cases and 50 controls are shown in Tables II and III. The number of observations does not always add up to 50, because in the first 9 cases and the first 11 controls Atkinson's latest method only was used. In the remainder both solutions and all six sites were employed. The tables are therefore based on the means of 520 different skin tests in 100 persons, but for want of space the individual measurements cannot be given here (see Haggie, 1949). In both cases and controls there was a

TABLE II.—*A Comparison of the Mean Values for Diameter of Weal in Inches, at Six Different Sites in the Cases and Controls*

	Ménière	Control	Ménière	Control	Ménière	Control	Ménière	Control	Ménière	Control	Ménière	Control
Sites:	1B	2A	3B	4A	5A	6B	1B	2A	3B	4A	5A	6B
Mean	0.57	0.57	0.56	0.53	0.68	0.56	0.6	0.6	0.6	0.61	0.57	0.57
Standard deviation	0.1	0.1	0.08	0.08	0.09	0.08	0.1	0.1	0.1	0.08	0.1	0.1
No. of observations	39	41	39	41	50	50	39	41	39	41	50	50

TABLE III.—*A Comparison of the Mean Values for Diameter of Flare in Inches, at Six Different Sites in the Cases and Controls*

	Ménière	Control	Ménière	Control	Ménière	Control	Ménière	Control	Ménière	Control	Ménière	Control
Sites:	1B	2A	3B	4A	5A	6B	1B	2A	3B	4A	5A	6B
Mean	2.08	2.16	1.98	1.96	2.09	2.06	2.1	2.1	2.0	2.0	2.0	1.9
Standard deviation	0.23	0.3	0.23	0.26	0.23	0.29	0.27	0.34	0.28	0.27	0.31	0.26
No. of observations	39	41	39	41	50	50	39	41	39	41	50	50

well-defined variation either side of the mean. The upper and lower limits of weal and flare were 0.4 to 0.9 in. (1 to 2.3 cm.) and 1.4 to 2.9 in. (3.6 to 7.4 cm.) respectively.

These figures show the mean values and standard deviations to be so nearly identical both in cases and in controls that it can be concluded that there is no difference between them. Further statistical analysis is therefore unnecessary. Even allowing that only 20% of the cases of Ménière's disease show an abnormal response, there should be enough observations here for a difference between the cases and controls to be apparent. In fact there is none.

Summary

Histamine skin tests have been performed by Atkinson's method, and certain modifications of it, on 50 cases of Ménière's disease and 50 controls.

The production of pseudopodic processes from the central weal in Ménière's disease is identical with that in the controls. The greater the number of injections made the more likely is it that a pseudopodic process will appear.

The mean values for the diameter of flare and weal are almost identical at every one of the six sites, and in this respect also there is no significant difference between the cases of Ménière's disease and the controls.

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THE ERYSIPELOID OF ROSENBAACH

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Erysipeloid infections of the hand are generally considered to be uncommon. This impression is supported by the scant references to the condition in many of the popular textbooks and by many of the recent papers dealing with the clinical aspects of the infection. However, it has also been suggested that this apparent rarity is due to frequent misdiagnosis (McNeill Love, 1949). Casualty officers working near meat and fish markets, slaughterhouses, and hotel districts are quite familiar with the disease and regard it as being by no means uncommon. In most of the reported cases the diagnosis has depended solely on clinical grounds, and it has been argued that, as the clinical picture is so typical, biopsy with subsequent isolation of the causative organism is neither necessary nor justifiable (Goodwin, 1950).

Biopsies were performed in a number of the cases reported in this communication, and the results of this bacteriological investigation will be detailed later.

Clinical Features

The clinical picture is a very typical one and was uniform in all our cases. The original description was published by Marrant Baker (1873), who named the condition "erythema serpens." We agree with the observations of Rosenbach (1887), who stated: "The symptomatology is characteristic, and anyone having once seen the condition can readily make the diagnosis."

The patient complains of pain and swelling of a finger or part of a hand. The pain is often severe, is made worse by the application of heat, and is described as throbbing or burning. A history may be elicited of a scratch or puncture of the affected part by a meat bone, fish bone, fish skin, or butcher's knife, perhaps as long as two weeks before the onset of symptoms, but often no definite history of trauma is obtainable. Symptoms may have been present for several days or even weeks before the patient attends for treatment. It has been noticed that patients in the present series attended earlier if one of their workmates had previously been infected and had received treatment. The employees of a firm of Continental butchers were prominent for their early attendance.

Examination reveals a moderately inflamed swollen finger or part of the hand. Some evidence of the original injury is often visible as a stretched greyish scar. The swelling involves both the skin and the subcutaneous tissue, the margin of the skin-swelling is well defined, and the area of affected skin is dusky in colour. Although the patient complains of severe pain, tenderness is nothing like so apparent as in pyogenic infections of a similar area. Quite firm palpation of the infected part is tolerated. Associated lymphangitis and lymphadenitis are uncommon, and it is probable that their presence is indicative of secondary infection. Systemic effects have been described, but are uncommon.

Erysipeloid is a self-limiting condition. It is subject to spontaneous remission and ultimate resolution without suppuration, physical signs being present usually for a period of three to four weeks. Incision of the infected area benefits neither symptoms nor progress, and may result in secondary infection.

Clinical Cases

Two series of cases collected at King's College Hospital during 1948 and 1949 are reported. All presented the clinical features already described. The patients in the 1949 series were subjected to biopsy, and attempts were made to recover the causative organism. In three instances (Cases 2, 6, and 11) penicillin had unfortunately been administered before the biopsy was performed.

It will be noticed (Fig. 2) that no case was recorded during the first five months of 1949. This may have been due to failure to recognize the condition during this period. A search through the records, however, failed to reveal any hand infections with suggestive physical signs presenting at this time.

1948 Series

Thirty-one cases were seen which conformed to the clinical picture described. The seasonal incidence is shown in Fig. 1. The occupations of the patients were: housewives, 8; fishmongers, 8; butchers and poulterers, 6; bacon cutter, 1; unrecorded, 8. A

FIG. 1.—Monthly incidence of cases, 1948 series.

definite history of trauma from a possible source of infection was obtained in 12 instances. Eleven other patients admitted to the frequent occurrence of such trauma but were unable to implicate a specific instance. The possible sources included beef, mutton, and pork bones, poultry and rabbit bones, fish bones, and meat knives. Skate was the fish most often blamed. The duration of symptoms before attending hospital varied from one day to six weeks.