HAY FEVER: ITS IMMUNOLOGICAL MECHANISM, DIAGNOSIS, AND TREATMENT

BY

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Hay fever is a type of paroxysmal rhinorrhoea due to hypersensitivity to the pollen of the grasses. The well-known symptoms are produced in the sensitive subject by the application of pollen to the upper respiratory tract and eyes. Normally this occurs only during the pollinating season of the grasses (early summer), when the widely disseminated air-borne pollen reaches the sensitive person, but the same symptoms can be produced artificially at any other time of the year by applying preserved pollen or pollen extract to the mucous membrane. This condition is frequently referred to as "seasonal hay fever" in contradistinction to "perennial hay fever," a type of paroxysmal rhinorrhoea due to hypersensitivity to non-seasonal products such as animal dandruffs, orris root from face powder, etc.

This loose usage is confusing and undesirable, and the term "hay fever" should be confined to hypersensitivity to grass pollen, as Noon and Freeman have always recommended. True, the term is often applied in America and some other countries to paroxysmal rhinorrhoea caused by the ragweeds (absent in this country), but this is usually and more fittingly described as ragweed fever. The pollens of trees, weeds, and flowers are rarely a cause of paroxysmal rhinorrhoea in this country, although the autumn compositae (particularly the Michaelmas daisy) do produce a few cases (Freeman²).

The Immunological Mechanism

When pollen extract is applied to the skin of the hay-fever subject the following changes take place at the site of contact: (1) primary dilatation of the minute blood vessels; (2) increased permeability of the vessel walls leading to exudation of plasma; and (3) reflex dilatation of the surrounding arterioles. This has been shown by Lewis^{8, 9, 10} to be the mechanism of the allergic reaction, and incidentally the reaction of the skin to a variety of other forms of cellular damage. These changes are most conveniently demonstrated in the hay-fever subject by placing a drop of pollen extract on the skin of the forearm and pricking the skin with a needle through the drop; the well-known urticarial wheal and a surrounding erythema develop in ten to fifteen minutes. The normal skin is insensitive to such treatment with pollen extract.

The amount of pollen required to produce a well-marked reaction to the hay-fever subject's skin is exceedingly minute, a few millionths of a gram of dried pollen or its equivalent amount of extract. The symptoms vary with the locality of the sensitized tissue acted upon by the extract; thus urticaria is produced in the skin, asthma in the lungs, hay fever in the upper respiratory tract, etc. If a suitable dose of pollen extract is given intravenously to a hay-fever case the active principle of the extract is carried round the body by the blood, and urticaria, asthma, hay fever, and certain other conditions result simultaneously.

When a small quantity of serum from a hay fever subject is injected into the skin of a normal person, the serum is rapidly absorbed and the skin resumes its normal appearance. Subsequently, on injecting pollen extract into the same area, a wheal and erythema develops identical with that seen on injecting the extract into the

skin of the hay-fever subject. If, instead of injecting the extract into the site of the serum injection, it is injected (in suitable quantity) subcutaneously or intravenously in a distant part of the body, the active principle is carried round in the blood and produces the same reaction at the site of the serum injection.

This transfer of hypersensitivity to the skin of normal persons was first described in 1921 by Prausnitz and Küstner.¹¹ Cases have been recorded of blood transfusion from hypersensitive individuals to non-sensitive persons leading to a condition of general hypersensitiveness in the latter. The property of serum from the hypersensitive subject to sensitize normal skin is assumed to be due to the presence in that serum of a sensitizing antibody, the allergic reagin or allergin, which has been aptly named "idioceptor" by Freeman.³ When idioceptor is attached to tissue cells the latter produce the allergic reaction on contact with the active principle of the specific reaction-producing substance (the allergen, atopen, or more fittingly "idiotoxin").

When a passively sensitized skin site is acted upon by the specific idiotoxin in sufficient quantity to elicit the maximum reaction, the site becomes desensitized—that is, the idioceptor is inactivated or destroyed, and the site does not give any reaction to further treatment with idiotoxin. If, however, a submaximal dose of idiotoxin is given in the first place, some idioceptor escapes inactivation, and a second reaction can be produced by another injection of idiotoxin (Harley⁴). If a mixture of idiotoxin with idioceptor is injected into the normal skin the ensuing reaction is similar to that in which the idioceptor is injected first and the idiotoxin after an interval, though the former reaction develops more slowly.

Incubating such mixtures at 37° C. for various periods was found to be without effect on their power to produce reactions in normal skins; it appears that idioceptor and idiotoxin are not mutually inactivated *in vitro*, though it has been shown that a definite linkage occurs.⁶ The inactivation of idioceptor by idiotoxin takes place only *in vivo*—that is, by allergic reaction involving tissue cells. The reaction of the sensitized skin to the specific idiotoxin is similar to, if not identical with, that of the skin to histamine (Lewis^{8, 9, 10}), and modern opinion is that histamine itself is liberated from the sensitized cells by the action of idiotoxin on the latter, and this histamine produces the actual changes in the blood vessels and smooth muscle fibres which constitute the allergic reaction. The liberation of histamine by the cells is the result of damage to them, and the allergic reaction is simply the expression of cellular damage produced by the special method of specific idiotoxin-idioceptor union on or in the cells.

The desensitization of hay-fever patients by repeated injections of pollen extract is the result of inactivation of idioceptor, as shown by the abolition of the patient's skin sensitivity and serum idioceptor. Specific desensitization is a series of mild extensive allergic reactions, and therefore entails the repeated liberation of histamine in the body by the action of renewed doses of pollen extract on the sensitized cells. This process might be expected to bring about an increased tolerance of the body to histamine. In view of these considerations the histamine skin reactions of a series of twenty hay-fever cases were measured before, during, and after a course of desensitizing injections of pollen extract. It was found that the reactions to histamine were not in any way diminished by the treatment, though the reactions to pollen extract progressively diminished. At first sight this result seems to discredit the histamine-tolerance theory, but when one considers the fact that histamine is believed to be an agent necessary for the physiological adjustment of the tone of the blood vessels, one could

not have hoped to find such a profound change of the blood vessels of the skin after desensitization with pollen extract as would have been entailed by a reduced skin reaction to histamine. The above result, therefore, does not in any way invalidate the histamine theory or lessen the probability that the histamine tolerance of the body as a whole may be increased.

One very interesting fact which sheds some light on the question from another angle, and which was first reported by Freeman¹ in 1930 and has been confirmed frequently since then at St. Mary's Hospital Asthma Clinic, is that a hay-fever patient who exhibits also a skin sensitivity to, say, egg or horse idiotoxin, on being thoroughly desensitized to pollen, has the skin reaction to egg or horse definitely reduced, but this regains its former intensity after a few weeks. Now, if a normal skin site is sensitized with serum containing idioceptors for both pollen and horse idiotoxins and desensitized to pollen by one injection of pollen extract, the site retains its full sensitivity to horse extract; also, the injection of pollen into a site sensitized to horse alone does not diminish its subsequent reaction to horse extract, nor does pollen extract have any desensitizing effect on the patient sensitive only to horse. The actual desensitization, therefore, is strictly specific, yet, as stated above, the repeated injection of pollen extract in a patient showing sensitivity to both pollen and horse leads to diminution of reaction to horse in addition to loss of reaction to pollen.

The only feasible explanation that presents itself to account for the non-specific action of a process which is apparently strictly specific, in view of the absence of any decrease of the reaction of the skin to histamine, is that the sensitized skin cells as the result of repeated trauma by one specific idiotoxin-idioceptor union in the cells develop a temporary increase of resistance to trauma of the same type produced by other specific idioceptor-idiotoxin unions. Thus, when the horse-pollen-sensitive patient is thoroughly desensitized with pollen extract and then tested with a quantity of horse extract equal to that used before the desensitization course, the skin cells, though still containing their full complement of horse idioceptor, suffer less damage by the horse idiotoxin-idioceptor union and liberate less histamine, causing the blood vessels to give a diminished skin reaction. This process might account also for the clinical improvement, frequently reported, produced by peptone and other forms of non-specific treatment in allergic cases.

Development and Nature of the Hypersensitive State

On this question there are but few facts available. One proven point is that sufferers from hay fever and other forms of allergic manifestation have very frequently a family history of allergy. The particular clinical condition is not necessarily inherited, the actual inheritance being the capacity to develop the hypersensitive state, and called "the allergic diathesis" for want of a more informative name. The exact nature of the immunological or biochemical link which produces the actual sensitization in the individual with an allergic inheritance is so far unknown.

One point which may have a bearing on the matter has been reported (Harley⁴): the blood of non-sensitive persons readily lyse the "granules" of Timothy pollen, but the blood of hay-fever cases is deficient in this respect. As the method of preparation of the granule suspensions entailed the almost complete loss of idiotoxin, the meaning of this difference of lytic power is not obvious. Only one non-hay-fever patient in the series of twenty-four cases examined had blood deficient in this lytic power; skin tests to pollen were negative; there was no history

of allergy in the antecedent family history or in that of the patient's husband, but the information was volunteered that her daughter suffered from hay fever. As the latter was not available for skin testing the "coincidence" loses much of its interest. On the other hand, that the capacity of a hay-fever patient's serum to sensitize a normal skin does not appear to be due directly to a deficiency or lack of any substance or property in that serum, but to an additional substance or property (the alleged idioceptor), is supported by the observation that the sensitizing power of such a serum is not in any way diminished by prolonged incubation at 37° C. when mixed with normal serum.

The ease and certainty with which hay-fever serum sensitizes a normal skin is in sharp contrast to the repeated failure of numerous workers to transfer the sensitive state to the lower animals by the injection of serum from the human hypersensitive. This led to testing the effect of rabbit serum on the sensitizing power of hay-fever serum. The latter was mixed with an equal volume of rabbit serum and incubated at 37° C. for one hour; a control mixture of hay-fever serum with normal saline was treated in a like manner. Equal volumes of both preparations were injected into two skin sites of a normal man. The following day 20,000 units of pollen extract were injected subcutaneously in the leg, and fifty minutes later a wheal with erythema developed at the site of the injection of the hay-fever-serum-saline mixture, but no change was observed at the site of the hay-fever-serum-rabbit-serum injection. This result was obtained in three normal persons. (The same subject was not suitable for repeat tests, as a condition of sensitivity to rabbit serum was liable to develop and obscure the results (Harley⁵).) As rabbit serum was found to be without effect on the idiotoxin of pollen extract, it appears that rabbit serum contains some factor capable of inhibiting or inactivating the hay-fever idioceptor. The nature and significance of this factor remain to be determined.

Diagnosis

The rhinorrhoea is coincident with the pollinating season of the grasses; in the average case of uncomplicated hay fever the symptoms begin about the third week in May and continue until the middle of July, the patient being free the remainder of the year. The symptoms consist of intense irritation and swelling of the mucous membrane of the nose, with paroxysms of violent sneezing (frequently as many as thirty to forty in rapid succession) accompanied by profuse serous discharge, which leaves the patient quite exhausted. There is also itching of the eyes with congestion of the conjunctivae and lachrymation. Asthmatic symptoms are not infrequently present, especially towards the end of the season, and these tend to increase in intensity and during each successive hay-fever season. The symptoms vary considerably with the weather and the locality; dry, sunny weather and proximity of pollinating grass increasing them, and rain and the still air in closed rooms, etc., tending to lessen them by decreasing the amount of pollen in the air. Grass pollen, being very light and borne by the air for great distances, makes it almost impossible for the sufferer to escape contact. As in other allergic conditions the immediate alleviation of symptoms produced by the injection of adrenaline is of diagnostic value.

SPECIFIC SKIN REACTIONS

The diagnosis is confirmed by producing a skin reaction with pollen extract. Freeman has shown that the idiotoxins of all the commonly occurring grasses are closely similar, and that Timothy pollen extract is the most

satisfactory for skin testing. The method of testing employed at the St. Mary's Hospital Hay Fever Clinic is the "prick" method (Freeman,¹ Harley⁷): a drop of pollen extract is placed on the skin of the forearm or leg and the latter lightly pricked with a hypodermic needle through the drop. The drop is then wiped off with cotton-wool. For routine testing two dilutions of pollen extract are used, 5,000 and 50,000 units per c.cm. respectively. If the patient is sensitive—that is, a true hay-fever sufferer—whealing and erythema develop about the site of the skin puncture in ten to fifteen minutes. This method has been found to be more convenient and exact than either the intradermal or the scratch method.

DIFFERENTIAL DIAGNOSIS

The characteristic type of symptoms, the periodicity, and the evidence of the skin tests usually make it easy to differentiate hay fever from the common cold, chronic infective nasal catarrh, and paroxysmal rhinorrhoea due to causes other than pollen.

Treatment

The most satisfactory treatment of hay fever is that of specific desensitization by a course of subcutaneous injections of Timothy pollen extract controlled by skin tests (Freeman,^{1 2 3} Harley⁷). The doses are usually increased by 15 per cent. each time, and the amount of treatment required varies from case to case. If treatment is continued until the skin reactions and serum idiocaptor are abolished complete relief of symptoms can be guaranteed. However, it is often found that satisfactory clinical results are obtained by a course of treatment shorter than that necessary to abolish completely the skin reactions. The injections are given most conveniently at intervals of two to three days during the months of April and May, but the rate of administration can be varied within wide limits. Freeman has perfected a method of "rush inoculation" by which the patient can receive the whole course of injections in less than a week, but careful and constant supervision by the medical man is necessary.

The next best method of treatment, should the patient present himself for treatment after the hay-fever season has started, is that of small daily doses of pollen extract combined with adrenaline. Many non-specific methods are often advocated, such as nasal ointments, sprays, douches, etc., and may give some relief in mild cases, especially those preparations containing adrenaline, but the effect is of short duration. As stated above the treatment of choice is specific desensitization with Timothy pollen extract, which gives practically 100 per cent. relief in all cases.

A word may be added, in conclusion, on the necessity of making skin tests for diagnosis and treatment. Last year a patient presented himself for treatment who was alleged to suffer from hay fever and who had received several courses of injections of pollen extract with no relief of symptoms; skin tests had not been made. The patient complained of attacks of sneezing, accompanied by nasal discharge, aggravated by dusty warm weather but occurring at intervals at all times of the year, and a general feeling of "stuffiness" of the nose between attacks. The history made one doubtful of the diagnosis, and skin tests with pollen extract were found to be negative. The condition was one of chronic nasal catarrh due to a streptococcus, with a hypersensitivity to the products of that organism, which explains the lack of improvement by injections of pollen extract. The condition cleared up with autogenous vaccine treatment.

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THE TREATMENT OF CEREBRO-SPINAL FEVER

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Historical Survey of the Malady

Cerebro-spinal fever was first differentiated by Vieusseaux, in Geneva, in 1805. Danielson and Mason recorded an outbreak in Massachusetts in 1806, since when various manifestations of the disease have been recorded at intervals. In 1887 Weichselbaum gave a full description of the diplococci found in the direct smear of meningeal exudate observed post mortem in people who succumbed to meningitis. In 1896 Heubner was the first to demonstrate meningococci in cerebro-spinal fluid obtained from a living person. The most beneficial contribution was probably the discovery of anti-meningococcus serum by Jachmann in Germany and by Flexner in America, and the introduction of the intraspinal injection of the serum by Flexner in 1904.

Outbreaks of the disease were being recorded from nearly all parts of the world, with the result that towards the end of the nineteenth century cerebro-spinal fever had become—or at least was generally recognized as—a cosmopolitan disease. Except for two or three small epidemics recorded in London and Rochester, this country was comparatively free until the early part of the present century. The first serious outbreak in the British Isles occurred in Glasgow in 1907-8: there were 1,238 cases, with 838 deaths. About the same time the disease was prevalent in Belfast, where there were 725 cases.

The disease was made notifiable in 1912, and the following table shows the incidence since that year.

Year	Notified Cases	Registered Deaths
1912	104	142
1913	305	163
1914	315	194
1915	2,566	1,974
1916	1,306	1,214
1917	1,465	1,531
1918	798	812
1919	848	573
1920	583	412
1921	411	416
1922	344	360
1923	301	284
1924	397	301
1925	402	354
1926	385	365
1927	470	430
1928	412	438
1929	650	588
1930	664	638
1931	2,157	1,440
1932	2,095	1,199

The increased prevalence of the disease amongst the civilian population during the war years was a striking feature, and coincided with the outbreaks in the Army, where there were 4,238 cases, with 1,928 deaths, in the Home Commands from 1914 to 1918.