

# HAY FEVER; RECENT INVESTIGATIONS ON ITS CAUSE, PREVENTION, AND TREATMENT.

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**PART I.***Introduction.*

HAY FEVER is a disease which on account of its peculiar interest has attracted the attention of the medical world ever since it was first accurately described by Bostock of London in 1819. To what extent the disease occurred before his time is difficult to determine; but from the fact that his observations were at once confirmed by a number of contemporary medical men it is probable that at the time of his writing it was not very uncommon. We have no exact knowledge of the existence of the disease in England prior to the nineteenth century, and indeed many authors hold that the chief etiological factors were not present in earlier times. It is my purpose in this paper to discuss the researches recently carried out by Prof. Dunbar at the State Institute of Public Health in Hamburg, which have very considerably increased our knowledge of the interesting malady, and have also narrowed the field for its future investigation.

Hay fever occurs yearly in individuals, with an inherited or acquired predisposition, only at a definite period of the year, and not outside of that period. In England, Germany and other countries of middle Europe it appears about the middle of May, and lasts until about the end of July; whereas in the United States of North America the disease is seen at different periods, *e.g.* in the Northern States it occurs typically in the early summer, and again in the autumn, the earlier form being called 'June cold' or 'Spring catarrh,' and the later is known as 'Autumnal catarrh,' which beginning in August or September lasts until the first frost. In the Southern States and notably in New Orleans cases are met with all the year round. The reason for these differences will be apparent when the etiology has been considered. Whenever the season is passed the symptoms disappear, and the patients may count on ten or eleven months of perfect immunity from the disorder. While the hay-fever season reigns, on the other hand, the sufferers pass a very miserable time, being quite incapable of attending to business affairs, and unable to enter into any of their usual amusements, since the slightest exposure in the summer air may bring on the symptoms of the disease. The illness is indeed of no trivial nature, especially when it occurs as a complication of graver diseases, and means to combat it successfully will be a god-send to the

many thousands of patients who otherwise look forward with dread to the most charming season of the year.

The symptoms of hay fever, which are apparently very similar wherever the disease occurs, are somewhat as follows:—A few weeks before the hay-fever season approaches, the patients notice at times a slight feeling of itching in the eyes and nose, and transient slight catarrh of the upper air passages. Then one day there comes on suddenly, either a sneezing fit, or else a strong feeling of itching and burning in the eyes and nose, followed by most profuse lachrymation and rhinorrhoea. Fluid positively streams from both eyes and nose, and it is no exaggeration to say that in certain cases four or five handkerchiefs in as many minutes are one after the other soaked with secretion. The sneezing fits are of most remarkable intensity, not one or two isolated sneezes, but paroxysms of the most painful kind, which the patient is quite unable to control. The inclination to rub the itching parts is irresistible, and there soon follows marked injection of the conjunctival vessels, with all the symptoms of acute conjunctivitis. The eyes become hot and red: this is followed frequently by chemosis, and the lids become so swollen that the patient can scarcely see. Later there appears swelling and congestion of the nasal mucous membrane, so great as to completely prevent the passage of air through the nose. Longer exposure in the hot dusty summer air leads to a spread of the process. There is itching of the gums, which makes many patients grind their teeth most unpleasantly, also intense itching of the fauces with short dry cough. A few notice a sharp pain in the ears. As the process increases in intensity, it spreads in some patients to the deeper air passages, causing a feeling of oppression in the chest, and symptoms more or less of an asthmatical character. This asthma, in severe cases, has been known to produce emphysema, and constitutes by far the most troublesome and dangerous symptom. Besides these symptoms every hay fever patient has during the attacks a very great feeling of lassitude and particular irritability of temper, and suffers also frequently from headache and sleeplessness. Of less common phenomena may be mentioned urticaria-like skin rashes attended with great itching. Fever as a rule is not present, although it does occur to a certain extent in some cases. The severity of the attacks depends to a great extent on the weather. In rainy weather the troublesome symptoms quickly disappear, and do not return so long as the surface of the ground remains damp. By staying in rooms with the doors and windows kept shut the attacks are less severe and less frequent. In localities with scanty vegetation

and at the sea-coast hay fever only very exceptionally occurs. It appears in its worst form after enforced exposure in the streets and dusty roads in hot, sunny weather, and very particularly on railway journeys after sitting by an open window.

The symptoms of hay fever are more apt to call forth the ridicule than the sympathy of onlookers, and it is a well-known fact that patients are too often made the laughing-stock of their friends. Yet it must not be forgotten that this malady becomes of grave moment when it occurs as a complication of more serious diseases. The nervous symptoms, for instance, may, and often do greatly aggravate cases of neurasthenia. The sneezing and cough, and even more the asthma and emphysema, necessarily become a great danger in cases of heart and lung disease. Physicians realise only too well the grave significance of hay fever in elderly patients with arterio-sclerosis. Cases of phthisis are known to be most injuriously affected by the frequent coughing and by the stress of the sneezing fits. In one case of latent phthisis a recrudescence of the disease was observed whilst the patient was suffering from hay-fever attacks. We shall refer later in detail to this case.

#### *Some Factors in the Etiology.*

*Geographical Distribution.* As regards the distribution of the disease, accurate statistics of the relative number of cases in the different countries are difficult to obtain, partly owing to faulty diagnosis, and partly to the desire of many patients to conceal the fact that they suffer from it, fearing to be considered neurasthenic. It was formerly said that the disease chiefly affected the Anglo-Saxon race, and indeed the majority of cases appear still to occur in England and America. It is rare in the north of Europe, and the number of patients in France, Russia, Italy, and Spain appears not to be very large. In Holland there are more, and in Germany, judging from the correspondence to be later referred to, and from the fact that there has been founded a Hay Fever Association of Heligoland with already about three hundred members, the number of cases would seem to be considerable. Indeed it has been said that at the present day there are in every large town in Germany almost as many hay-fever patients as in the Heligoland Association. Cases are not known to occur in Asia or Africa outside the European population.

*Heredity.* The influence of heredity is marked in the disease. In Beard's<sup>(6)</sup> experience it was a factor in 33% of his cases. Instances of

the transmissibility of the hay-fever predisposition have been recently observed, where the disease has been acquired by an adult belonging to a family not previously affected by it, and where the patient's children already show unmistakable signs of the disease.

*Sex.* It is the general opinion of authors that as a rule more men than women suffer from hay fever, the proportion being about 2:1; but statistics on the matter are not at all satisfactory.

*Age.* The disease has been observed to appear as early as the second year, and as late as the sixtieth; but most of the cases occur between the years of ten and forty. The disease belongs rather to the early and middle periods of life, but it is noticed that as a rule the attacks gradually increase in severity as age advances. A certain number of patients however apparently have the opposite experience.

At any rate in the majority of cases it does not appear materially to influence the prospect of a patient's longevity.

*Constitution.* It has already been said that hay fever occurs in persons with an inherited or acquired predisposition, and this predisposition is one of the most remarkable and interesting features of the disease; yet although much information on all the circumstances of a very large number of hay-fever patients has already been collected by different authors, in particular by Phoebus of Giessen<sup>(26)</sup>, and Beard<sup>(6)</sup> of New York, definite conclusions as regards the nature of the predisposition have not been arrived at. It is only therefore possible to pass in review certain facts and opinions having a bearing upon the subject.

*Temperament.* Most authors hold that hay fever occurs in those of active energetic type, yet a few maintain with Wyman<sup>(25)</sup> that it attacks persons of all temperaments.

*Education and Social Position.* A high degree of mental development has evidently a marked influence in predisposing to the disease, since the great majority of cases occur amongst the educated, and in people of good social position. In opposition to this view some hold that it passes unnoticed amongst the poor, who are not given to accurate observation. Those, however, who have seen the disease, and still more those who suffer from it, hold that the symptoms of real hay fever can scarcely escape observation.

*Suggestion.* We find others, who did not differentiate the disease sufficiently from nervous coryza, believing that hay fever is caused, and can be brought on by pure suggestion. Of recent observers Thost<sup>(24)</sup> of Hamburg made a careful enquiry into the complaint, noticing the

frequency of its occurrence amongst men of learning, especially after severe bodily and mental exertion, also its establishment in cases of exhaustion following many of the infectious diseases, particularly after influenza, and its occurrence after difficult labours.

A number of authors, *e.g.* Gueneau de Mussy and Molinié<sup>(21)</sup>, regarded the special predisposition to hay fever as the outcome of a gouty or arthritic diathesis. These diatheses are indeed present in many instances, and in England especially gout and hay fever are frequently found in association amongst the rich and better educated; but hay fever cannot be explained as the result of the gouty diathesis, for the disease occurs in very many who have no gouty tendency. Thost<sup>(22)</sup>, for instance, in an examination of 400 cases found a gouty disposition only in thirty.

#### *Former Theories of the Etiology.*

Hay fever affords yet another illustration of the familiar fact that the number of theories concerning the etiology of a disease is in inverse proportion to the state of knowledge of the subject.

That the malady was the outcome of local abnormalities, or diseased conditions of the nose was the opinion of Daly, Allen<sup>(3)</sup>, Roe, and others. Many, amongst whom were Sajous, Hack<sup>(11)</sup>, J. N. Mackenzie<sup>(19)</sup>, and Fink<sup>(14)</sup>, held that a diseased condition of the endings of the fifth nerve was responsible for the symptoms of hay fever.

These pathological theories appear, at first sight, as quite possible explanations of the phenomena of the disease. The first of these, *viz.* that hay fever depends on gross structural changes within the nose, was critically discussed by Morell Mackenzie<sup>(20)</sup>. He showed that the theory is open to the following fundamental objections; that in the first place only an insignificant proportion of the many sufferers from nasal disease are hay fever patients; that in many of the worst cases of hay fever there is absolutely no evidence, objective or subjective, of disease within the nose, and lastly that this doctrine altogether fails to account for the limitation of the complaint to one, or at most two brief seasons of the year. The theory that the trigeminus is responsible for the disease will be discussed at a later stage.

Most of the theories summarised above were formulated to explain the manifest predisposition that the hay-fever patient has to his complaint. As to the exciting cause which regularly every summer brings on the illness, there was a like diversity of opinion amongst

former observers. A micro-organismal theory was proposed by Helmholtz. Foremost amongst his many followers was Sticker<sup>(27)</sup>, and of late Heymann and Matchusita<sup>(28)</sup> have made observations on the same lines. It was natural from a study of the symptoms and character of the disease that the theory of mechanical irritation of a specially sensitive mucous membrane should have been widely entertained. Bostock<sup>(7)</sup>, Phoebus of Giessen<sup>(26)</sup>, and Beard<sup>(6)</sup>, amongst others, variously ascribed it to dust, bright light, heat, odoriferous substances, etc. The popular view was that the symptoms of hay fever are produced by emanations from hay, or by the pollen of grasses. Experiments with pollen, with the view of determining the value of this popular opinion, were carried out by two former observers. These were Elliotson<sup>(28)</sup>, who published his work in 1831, and Blackley<sup>(4)</sup>, whose researches were conducted about forty years later.

Elliotson believed that the disease does not usually appear "till the grass comes into flower, and as long as there is any flower remaining on the grass the disease continues."

Blackley examined the pollen of various grasses, and of plants belonging to thirty-five other natural orders. He devised a most ingenious method for counting the number of pollen grains in the air and found that in England 95% of the pollen contained in the atmosphere belongs to the Gramineae. His experiments were very carefully conducted. Pollen was applied to the mucous membranes of hay-fever patients, and was found to cause the same symptoms as in the natural disease, both in its catarrhal and in its asthmatical form. He concluded that hay fever is produced by the pollen of the grasses chiefly, but that a like power, with rare exceptions, was in some degree also possessed by the pollen of all the plants he examined. He believed the disturbance caused by pollen to be due partly to its mechanical, and partly to its physiological action,—the pollen tubes penetrating the mucous follicles, and thus giving rise to irritation. He further thought that volatile oil might be a constituent of the pollen, and might commence the disturbance. Finally he speaks of the valuable information which would probably be derived from a study of the chemical constitution of pollen grains, to determine whether there be not present "some powerful substance of the nature of one of the poisonous alkaloids, or some other equally powerful class of bodies."

A portion of the results obtained by Blackley were corroborated by experiments made by Morell Mackenzie<sup>(20)</sup> in 1887. These researches of Blackley, in particular, were thus very suggestive so far as they went,

and made a very valuable contribution to the knowledge of the subject: yet during a period of thirty years, after his work was published, although much had been written about the etiology of hay fever, and many new theories had been formulated, no really definite etiological factor explaining the peculiar phenomena of the disease in all cases was arrived at.

Now in approaching the study of the results of the most recent researches on the subject, we must agree with Dunbar's<sup>(6)</sup> proposition that correct conclusions in regard to the cause of hay fever will only be arrived at when it is possible to separate the factor completely from foreign elements, and by means of this factor, independent of temperature and meteorological conditions, and at a time of the year different from the real one, to cause all the symptoms of the disease, and that only in persons predisposed thereto.

#### *The Results of Recent Researches.*

Dunbar instituted experiments with the pollen of grasses, and other plants, in the spring of 1902. The results of these will now be reviewed.

Pollen of rye, carefully collected, free from bacteria, and applied to the eyes and nostrils of a large number of hay-fever patients, called forth *typical hay-fever symptoms*, both in the eyes and nose. These symptoms included photophobia, and a feeling as of sand in the eye, lachrymation, injection of the conjunctival vessels, oedema of the lids and even chemosis. The nasal mucous membrane became greatly swollen, along with much itching and rhinorrhoea. A large number of normal individuals were experimented on without any such effect.

That this action was produced by a specific poison in the pollen, and not by any hypersensitiveness of the trigeminus, according to the theory of J. Mackenzie and others above referred to, was proved by the fact that the same active pollen applied to the anal mucous membrane of a hay-fever patient, produced in that situation severe itching which lasted some hours. A similar experiment with a person not subject to hay fever was without result.

This specific irritation of the mucous membranes of hay fever patients was not excited by the mere mechanical irritation of the pollen, for rye pollen, which is particularly toxic, has a perfectly smooth outer surface, and other pollen examined, which had a prickly surface, did not give rise to the above reaction. Mechanical irritants of various



kinds, such as soot, dust, etc., were also experimented with, but characteristic symptoms were not produced in patients predisposed to hay fever by such means.

Many experiments were made to exclude the possibility of suggestion. At all times of the year, even in mid-winter, it was found that the disease could be brought on artificially in hay-fever subjects, through the agency of the pollen of certain plants.

These results, showing the peculiar specific poisonous nature of some varieties of pollen, are all the more interesting, as Dunbar<sup>(10)</sup> in commencing his investigations with the view of clearing up the obscurity of the etiology of hay fever, inclined to support the theory that micro-organisms set up the attacks; and indeed as the result of many examinations he found the continuous, exclusive, and abundant presence of certain bacteria, in the nasal and other mucous secretions of hay fever patients. Further observations however led him to disbelieve in the etiological significance of bacteria in the disease.

He suffers himself from hay fever, and noticed that attacks excited during the hay fever season promptly subsided when he withdrew himself into a room where all the doors and windows were shut, only to come on again after exposure in the open.

Observations of this nature were carried out on railway journeys during the hay fever season; attacks coming on after sitting by an open window, especially when the train was passing through the midst of cornfields in warm weather, and these attacks passing away when windows and ventilators were closed.

This disposed of the possibility of a micro-organismal infection, where growth and multiplication of the germs would certainly have led to an increase and not to a decrease of the symptoms when the entrance of outside air was discontinued.

Experiments with pollen were then instituted, with the highly interesting results already described. A further experiment of much interest was that in which two persons, one a hay-fever patient, the other not subject to the disease, were placed in a glass chamber. Each blew into a flat dish on which a small quantity of rye pollen had been placed. The hay-fever patient, after a deep inspiration, caused by the act of laughing, was attacked by cough, accompanied by dyspnoea with inspiratory stridor, and suffered for two days from bronchitis, with purulent sputum. The other person showed no symptoms of any kind.

Up to the present time the pollen of 130 different plants has been examined with regard to effects on persons liable to hay fever. The list

of 114 plants tested by Dr Kammann at the Hygienic Institute, Hamburg, which includes all those with toxic pollen, will be found grouped in the Appendix. He adopted the Linnean classification, and examined plants from most of the classes and most of the orders of that system. Plants with potent toxic pollen chiefly belong to the third, nineteenth, and twenty-first classes of this system. Of these pollens those of 25 grasses and only 7 of other kinds of plants (see Appendix) excite a positive action. In these other plants the pollen is not so potent as is that of the grasses. The pollen of rye was found to be most active. The pollens of all the other plants tested were without influence of any kind. They appeared to be quite inert. Experiments on the toxicity of different pollens are still being carried out.

Liefmann, in a research conducted in the Hygienic Institute, Hamburg, the complete results of which will shortly be published, confirmed Blackley's statement, that on days when attacks of hay fever are especially severe there is an unusually large amount of pollen in the air; that, in fact, the severity of hay-fever attacks is in direct proportion to the quantity of pollen present in the atmosphere. He further proved that the amount of pollen inhaled by a patient on days when hay-fever symptoms were present was more than sufficient to induce attacks; for it has been demonstrated that the quantity of toxin yielded by two or three pollen granules suffices to cause a distinct hay-fever attack in some predisposed subjects. Liefmann found indeed that on certain days a patient would inhale on an average from each cubic metre of air about 700 pollen grains.

#### *The Structure and Chemical Constitution of Pollen.*

A grain of pollen, examined microscopically, exhibits the characters of a simple cell, of definite and regular shape, averaging about 50—60  $\mu$ m. in length, whose contents are enclosed by a double membrane.

The outer coat, or exine, is pierced by one or more holes or slits, the pores, and is either smooth or more or less densely covered by minute and very fine protuberances. As has already been said, pollen, which has been examined and found active in inducing attacks like hay fever, has a smooth exterior; whilst the pollen whose outer membrane is rough, has been found to be inert. *Solidago* pollen is an exception, it having a rough surface.

The outer membrane of rye pollen is smooth. When treated with

Millon's reagent however it shows a reticular structure. It stains with aniline dyes. The inner coat, or intine, which remains unstained by iodine and aniline dyes, becomes distinct when treated with a solution of chromic acid. It is probably a cellulose membrane.

The contents of the pollen cells, which were found to be toxic, consist of granular matter that stains a dark blue with iodine solution and gives other reactions showing it to be of an amyloid character. This granular matter magnified five hundred times presents a very striking resemblance to bacteria, having the same form, size, and staining reaction; and such bodies found in nasal mucus of a hay-fever patient might very readily be mistaken for bacilli.

20 million rye pollen grains weigh about one gramme.

The chemical constitution has been thus estimated by Kammann, in air-dried rye pollen :

Water 10·18 % .      Organic Matter 86·4 % .      Ash 3·4 % .

The organic matter consists of fats, albuminous substances, nitrogen-containing substances not of an albuminous nature, carbohydrates, and enzymes. These latter are proteolytic and diastatic. The question as to whether the toxic reaction resulted from these enzymes was settled negatively by Dunbar as follows :—He had taken about five grammes of maize pollen with him on a journey. On the way this pollen became fluid, owing it was thought to bacterial decomposition. On this supposition a small quantity of carbolic acid was added to check bacterial growth. Experiments with this material at a later date showed that the pollen was quite inert, but that there were still active enzymes present. It was not found possible to destroy the ferments without also rendering the toxin inert. Attempts to distinguish by chemical means the toxins obtained from all the different plants with toxic pollen will probably not be possible.

Experiments at first seemed to show that the toxin was destroyed when exposed to a temperature of 70° C. These experiments were carried out by Dunbar at a time when only a very small quantity of pollen was available, and later investigations with larger quantities of pollen gave more accurate results. These results, showing the effect of different degrees of temperature on the toxin, may be tabulated as follows :

1.	Temperature 60—70° C.	No diminution in toxicity.
2.	"    70—80°	Toxicity now $\frac{3}{4}$ of original.
3.	"    80—90°	"    " $\frac{3}{4}$ "    "
4.	"    90—100°	"    " $\frac{1}{4}$ "    "

The effect of acids and alkalies on pollen toxin has also been ascertained. After being treated with sulphuric acid the proteid remained still very toxic. Alkalies had much greater effect in diminishing toxicity; they rendered the toxin nearly inert.

#### *Isolation of the Toxin.*

Following on the results showing the special toxic action of pollen an endeavour was made to isolate the poisonous constituent.

After destruction of the limiting membrane of the pollen grain, it was found that pollen becomes in great part dissolved in nasal and lachrymal secretions, in serum, and in physiological salt solution, kept at body temperature.

Pollen applied to the dried skin had no irritant action, but when the skin was moist with sweat then the pollen set up irritation with itching in subjects predisposed to hay fever.

It is unnecessary to enter into the details of the original experiments, but in brief the perfected process by which the toxin is obtained is as follows:—Pollen is extracted in saline solution at 37° C., for some six to twelve hours, and then precipitated with alcohol.

In the proteid obtained Kammann found that the globulin is inert, whereas the albumin is highly toxic. So toxic is it, that so small a quantity as a forty-thousandth of a milligramme of the common proteid, in solution, locally applied in the conjunctival sac of a hay-fever patient, is capable of causing itching and redness lasting for some hours. It was furthermore proved that the other constituents of the pollen grains, including the ethereal oils, do not possess this special action.

#### *Experiments with the Toxin.*

Toxin locally applied on a very large number of hay-fever patients and control subjects, produced, in the predisposed, characteristic hay-fever symptoms, subjective and objective, varying in amount, both in the eyes and in the nose.

The special action of the toxin is a yet further proof that the reaction is due to chemical, and not to mechanical agency. This is rendered still more obvious by the results of subcutaneous injection of toxin, which produced in a patient all the symptoms of hay fever, in typical and severe form. There were induced lachrymation, sneezing, cough, roughness of the throat, inspiratory stridor, and blocking of the

air passages, besides other even graver symptoms. Subcutaneous injection of the toxin in a control subject on the other hand produced no such effect.

Dunbar has thus brought forward convincing evidence that the exciting cause of hay fever in all the cases coming under his observation is a toxin contained in the pollen of certain plants, particularly in that of rye and other grasses.

Attention was then turned to the disease as it occurs in the United States of North America. There, as has been already said, hay fever appears in the different States at different seasons of the year. In the Northern States, for example, two forms are observed, one occurring in the early summer, and the other in the autumn. Dr Dunbar had the opportunity himself of experimenting with four American patients, who suffered while in America from the latter form (autumnal catarrh). These patients did not suffer from the attacks of the natural disease in Germany, at the time of its prevalence there. He found that they were not at all, or only slightly affected by the toxin obtained from rye, but were at once seized with severe and typical appearances of the disease when the pollen or the toxin from *Ambrosia* (Wormwood) and *Solidago* (Golden Rod), late-flowering American plants of rank growth, was applied in the same manner as in the other experiments to the mucous membranes of the eyes and nose.

#### *Preparation of Pollen Antitoxin.*

After isolating a toxin of such special nature Dunbar naturally endeavoured to obtain an effective antitoxin. This antitoxin was first obtained by injecting the pollen, later the toxin derived from the pollen of various grasses and other plants, into different animals, such as rabbits, goats, and horses. The animals reacted very differently to the poison, and young thoroughbred horses were as a rule found to be best suited for the purpose. The antitoxin obtained was capable of neutralising the toxin *in vitro*, so that a mixture of toxin and antitoxin applied to the conjunctivae of persons previously reacting to the toxin, now gave rise to no irritation. It was also found possible by means of the antitoxin to allay artificial attacks excited by toxin and pollen.

A question of great importance, on which the practical possibility of treating the disease successfully by means of the antitoxin depends, is whether the toxins of the various pollens proved active are alike? Although not identical it is certain that they are very closely related

to one another, for it is found that antitoxin obtained from the pollen of one sort can neutralise, though not always in the same degree, toxins derived from other pollen. The toxic proteid for instance from *Solidago* pollen was neutralised *in vitro* by maize pollen antitoxin. This was also demonstrated in cases of American autumnal catarrh, where the artificial attacks induced by the *Solidago* pollen were allayed by means of pollen antitoxin obtained from the Gramineae. It is of further interest that irritant symptoms of varying intensity were also produced in six hay-fever patients in Germany, when the pollen or toxin of *Solidago* and *Ambrosia* was applied to their conjunctivae, and that these appearances were quickly removed by means of maize or rye pollen antitoxin.

*General evidence that Pollen Toxin is the exciting cause of Hay Fever.*

In seeking a confirmation of these important results specimens of pollen and of toxin and antitoxin were sent to medical men, not only in Germany, but also in England and Scotland, Denmark, and various districts of the United States of North America, *e.g.* to New York, Baltimore, St Paul, Minn., and St Louis, in the more northerly part, and to New Orleans which represents the southern climate. Some of the observations thus made have already been published, while others have been privately communicated.

In *Great Britain*, careful experiments were carried out by Sir Felix Semon<sup>(22)</sup> in London, and Dr McBride<sup>(18)</sup> in Edinburgh. The first-mentioned made observations both with toxin and antitoxin on five hay-fever patients and seven control subjects, with results corroborating Dunbar's. Two of the controls, it is true, also reacted slightly to the toxin. One of these suffers from asthma, and is hypersensitive to wind and dust, while the other says he is liable to sudden violent paroxysms of sneezing, with considerable rhinorrhoea, especially in the early morning at any time of the year.

Dr McBride experimented with four hay-fever patients. Three of these gave very typical reactions to the toxin. The patient who did not react suffers from similar attacks in winter. There was no reaction in the two control subjects. These results are also borne out in communications from the other sources, where all the cases tested reacted to the toxic pollen and testified to the efficiency of the antitoxin, both as regards neutralising the toxin *in vitro*, and cutting short attacks artificially excited. Control subjects were used in all cases.

All the cases experimented with reacted to the toxic pollen: a few showed no reaction to the toxin itself. This had also been observed in laboratory experiments with dilute solutions of toxin. On increasing the strength of the toxin, however, typical symptoms were produced. It is therefore extremely probable that outside cases would have also reacted to a toxin less dilute or more fresh. Quite recently several eminent specialists in Hamburg have privately communicated the information to us that the results of their experiments with a number of hay-fever patients confirm Dunbar's view of the etiology.

Of great interest is a letter from a doctor in Egypt, who, while engaged in collecting maize pollen, visited a friend who suffered regularly at the time when maize flowered there from persistent 'cold in the head,' especially marked when he made railway journeys. He had not been with him many minutes when his friend developed a perfectly typical attack of hay fever. On another occasion to put the matter to the test this gentleman snuffed some maize pollen up the nose. After a few seconds he was attacked with severe sneezing, and an intense catarrh, with swelling of the nose, profuse lachrymation, and smarting in the eyes. These symptoms lasted three days, and were so bad as to prevent his sleeping at night. No antitoxin was available, and the patient could not be induced to repeat the experiment! He also tried the effect of maize pollen on three control persons, who experienced no symptoms.

Some of the results obtained *in America* have been published by Mayer<sup>(16)</sup> of New York. These results, and the others found in the correspondence, make it very probable that the early spring form in America, the so-called 'June cold,' is identical with typical European hay fever, and is produced by the pollen of grasses.

Autumnal catarrh is apparently the most common form of the disease there, and, as has been mentioned, is popularly believed to arise from the pollen of such late-flowering plants as 'Golden Rod' and 'Wormwood.'

Of all American cases on which pollen and toxin were tested only three suffered from the early form of the disease, the 'June cold.' Two of these gave typical reactions to maize pollen toxin. The third showed no irritation. It is probable that the toxin used in this case was not fresh.

In a number of cases of autumnal catarrh experiments were made with toxin obtained from maize and from barley. Most of the cases were insusceptible to these toxins. One was irritated by the barley

toxin. All of the cases reacted which were tested with *Solidago* (Golden Rod) pollen, and toxin respectively.

Antitoxin (obtained by means of pollen of plants belonging to the Gramineae) was used in six cases, always with prompt beneficial result.

Autumnal catarrh, therefore, differs from European hay fever only in not being excited by the pollen of the grasses, but instead by the pollen of *Solidago* and *Ambrosia*, and possibly other late-flowering plants. These patients pass the early summer free from all symptoms, and only show signs of the disease when autumn appears. That this autumnal catarrh has a close relationship, however, to European hay fever is shown by the fact that the symptoms of the disease can be subdued by the antitoxin for the pollen of graminaceous plants.

It is evident from the foregoing that a toxin isolated exclusively from the pollen of certain plants is able to call forth in hay-fever patients, in all civilised countries, independent of the season, typical attacks of the disease. Conversely, we may conclude that hay fever as it occurs in the different civilised lands is really an etiologically identical disease, so far as the exciting cause is concerned. What it is that brings about the hay-fever predisposition is a subject of much greater difficulty, and will not be entered upon in this paper.

So constant have been the reactions shown by hay-fever patients to pollen toxin, that this toxin may have a distinct value as a *diagnostic agent*. Especially valuable will it be to the practitioner in discriminating from hay fever such cases as those of coryza nervosum, and many catarrhal ailments closely resembling hay fever except in its peculiar periodicity. Cases of pure asthma could by this means also be differentiated.

Such observations with pollen toxin have already been made, and this use of it recommended to the profession by one or two specialists, including Dr Thost of Hamburg.

It is now proposed to consider in how far treatment by pollen antitoxin is likely to be an important therapeutic advance on existing methods of treatment of hay fever.

Everybody admits that treatment in this disease has been up to the present time unsatisfactory. Many therapeutic methods have been proposed and introduced, with in certain cases apparently some measure of success. Such success however has usually been of a partial nature, or the method of treatment has been limited in application only to certain classes of patients. As is shown by very general practice the



great majority of sufferers find their only safety in flight to the sea or sea-coast, or away to certain mountainous regions where they remain until the hay-fever season is gone by. In these localities they can usually spend the days out of doors without using any of the remedies recommended. Of such remedies cocain has had a long trial, and is generally thought to be of most benefit. In this disease however cocain becomes a dangerous drug to use, on account of the frequent necessity for reapplication and the very common tendency of the patients to neurosis. In a very large number of cases cocain is found to be useless. Quinine is recommended by some: adrenalin has been much advocated by others. Morell Mackenzie found good results, he said, from insufflations into the nose of a powder consisting of a sixteenth of a grain of morphia and one grain of bismuth. More heroic treatment has been recommended. Cazenave was the first to cauterise the mucous membrane of the nose by way of lessening its susceptibility to hay fever. He used silver nitrate for the purpose. The electro-cautery has for the same reason been much employed.

The new treatment, founded as it is on a rational etiological basis, should, theoretically, provide a cure for all the symptoms of the troublesome malady, in all cases of the true disease. Hay fever being a disease arising in the predisposed from pollen toxin being inhaled by the patient from the air, if this toxin is neutralised before it has time to set up local irritation, or has entered the circulation, attacks of hay fever *should not arise at all*. An examination therefore into the results obtained from the use of the remedy in actual practice during last summer,—the first season of its introduction,—will be of the greatest possible interest.

## PART II.

### *The Results of Prevention and Treatment of Hay Fever by means of Pollen Antitoxin during the Summer of 1903.*

Through the courtesy of Prof. Dunbar the publications and private correspondence dealing with the general experience of doctors and patients in the summer of 1903 in regard to the value of the antitoxin were placed at my disposal, and I have been able, having critically examined these, to arrive at an estimate of the practical results of prevention and treatment in cases of the natural disease.

Before proceeding to an actual discussion of cases a few notes on the antitoxin will be given, with regard to its preparation and to the proper method of its use.

*Further Notes on the Preparation of Pollen Antitoxin.*

In sending out the serum, the greatest care was taken to ensure its sterility, the entire absence of all toxic properties, and the constancy of its antitoxic value.

1. The horses used for obtaining the serum were always under the inspection and control of a veterinary surgeon. Healthy horses were in all cases used, and the blood was withdrawn from them under aseptic precautions, and the after-manipulations with the serum were carried out with strict attention to asepsis. In order to make certain that no undestroyed pollen toxin remained in the serum, no blood was withdrawn from the horses until from six to eight days after they had perfectly recovered from the effects of the last injection of pollen toxin, and until they had regained their former weight. These effects after injection consisted in fever, loss of appetite and weight, and in local swelling. The serum was regularly tested to ensure sterility, and received an addition of  $\frac{1}{4}\%$  carbolic acid as preservative.

2. That the serum should always have a constant antitoxic value it was regularly standardised, and its power to neutralise pollen toxin estimated.

The method used for standardising serum is as follows:—Prof. Dunbar and Dr Prausnitz, both hay-fever patients, use the reaction of their conjunctival mucous membrane for the purpose of testing the strength both of toxin and antitoxin. The procedure is as follows:—In the first place a solution of toxin is chosen which just causes an unmistakable and typical reaction. Such a reaction is observed after a few minutes, and consists in subjective itching and feeling of heat, and objective reddening and swelling of the caruncle, plica semilunaris, and eyelids, of the eye treated. There is also injection of the limbus corneae, and of the conjunctival vessels. Then a series of mixtures of toxin and antitoxin are made, each containing that minimum toxic dose described above, along with decreasing quantities of antitoxin. The amount of antitoxin present in that mixture which just gives rise to no subjective or objective reaction is taken as a measure of the antitoxic strength. Frequently repeated experiments with this minimum toxic dose of pollen toxin show no marked decrease in the susceptibility of

the conjunctiva to this standard. Trials of other methods for standardising the serum are being made, but the one given has so far been found the most dependable. The antitoxic value of the serum does not apparently markedly diminish even after the lapse of several months.

The serum treatment of hay fever last summer was almost entirely confined to local applications to the conjunctival and nasal mucous membranes. The preparation used by patients was at first a fluid serum to which  $\frac{1}{4}\%$  carbolic acid was added as preservative. It was sent out in a sterile condition in small glass tubes each containing 2 c.c. An empty glass phial with a dropping pipette was also provided, so that it was only necessary to use a small quantity of the serum at a time. In spite of this precaution and of the addition of  $\frac{1}{4}\%$  carbolic acid the preparation very easily decomposed, and might be fit for use only for a few days after opening the tube. This decomposition was brought about by the frequent infection of the serum with germs from the air and from the nasal mucous membrane. A higher percentage of carbolic acid could not be used, as stronger concentrations gave rise to an unpleasant burning sensation in the eye; indeed a few particularly sensitive patients cannot bear even the  $\frac{1}{4}\%$  addition, complaining of severe irritation in the eyes and nose from the carbolised serum. On the other hand the addition of other antiseptics less irritating to the mucous membrane was for other reasons found to be impracticable.

This decomposition does not always occur, and can to a great extent be prevented by only using a small quantity of the serum at a time, and by carefully cleaning and sterilising the dropping pipette after use. When decomposition does set in it is evidenced by a uniform turbidity, and sometimes by the serum developing an odour. This of course renders the preparation unfit for further use. To be distinguished from this uniform turbidity is a slight flaky deposit in the serum, that is often present on despatch of the remedy in sterile condition. It arises from the carbolic acid present.

On account of the ease with which the fluid serum decomposes, and the sensitiveness of many patients to carbolic acid, Dunbar sought to produce a preparation that would obviate these difficulties, and be more convenient in application and surer in result. For this purpose he dried the fluid serum, and obtained a powder, that without the addition of any chemical preserved well for a long period. The drying took place in a large vacuum apparatus at a temperature of 40—45° C. The dried mass was finely powdered, mixed with sterile milk sugar, and strained through a very fine sieve. The resulting preparation was a

fine white, almost inodorous powder. All the operations were conducted under the strictest aseptic precautions, and bacteriological examinations which were regularly carried out guaranteed the sterility of the preparation.

*Method of use of Serum.*

The fluid serum is chiefly suited for local applications to the eye. By means of the pipette a drop of 'Pollantin,' as the preparation is called, is brought to the outer angle of the eye and allowed to touch the mucous membrane of the lower lid, which has previously been drawn down by the finger. A pleasant cool sensation in the eye testifies to the operation having been correctly carried out.

For the nose, the serum is best used in powder form. It is sniffed up each nostril in small quantity. The contained milk sugar lessens the irritation of the powder, and gives rise to a slight secretion of nasal mucus which helps to dissolve the dried serum. The advantage of using the remedy in powder form, in addition to its convenience in application, is that it enables the serum to be spread more efficiently over the whole inner lining of the nose, and to reach the recesses in the mucous membrane and the apertures of the neighbouring sinuses. Immediately after sniffing up the powder the taste of the milk sugar can frequently be appreciated, showing that the powder reaches even to the throat. The powder therefore reaches at least as far as the pollen that has been inhaled from the air and thus possesses a very distinct advantage over the fluid preparation.

Should it be desired to use the powdered serum also for the eye, a small quantity is applied to the conjunctival sac by means of a fine sterilised camel-hair brush. There is at first the feeling as of a foreign body in the eye which however passes off in about ten seconds and the beneficial effect follows very quickly. Many patients who were apparently not at all, or not sufficiently influenced, by using the fluid serum were able to keep themselves quite free from attacks by help of the dried preparation.

Especially in combating hay asthma was the dried serum found to be of great advantage, for it reached better the deeper air passages and was also better absorbed. In most cases the fluid serum only succeeded in reaching the front portion of the nasal mucous membrane, and was soon expelled from there by the profuse nasal secretion.

In studying the best means to use pollen antitoxin in the treatment

of hay fever the well-known fact found in practice with other sera must be borne in mind, that when antitoxin is brought into use, after the toxin has had time to enter into combination with the body cells, a hundred, or even a thousand times the amount sufficient to neutralise toxin *in vitro* may be quite useless in treatment. It is therefore clear that the greatest importance must be attached to the prophylactic use of the serum. For this purpose patients were recommended to sleep during the hay-fever period always with their bedroom windows shut, and to apply the 'Pollantin' regularly every morning a few minutes before getting up, both to the eyes and to the nose. By this means, according to experience, a patient can guard himself from attacks for several hours, often indeed for the whole day. Exposure in the open air should be limited to a few hours at most. It was further recommended that serum should always be used before going out into the open air, and before exposure to a probable great amount of pollen infection, as for instance before railway journeys. If in spite of such precaution the beginning of an attack be noticed, with slight itching or burning in the eyes or nose, serum should be at once reapplied, in order to check the further spread of the process by neutralising the pollen toxin so long as it remains local. It is perfectly obvious that a good result cannot be expected from use of serum when the process has been allowed to go on till a severe nasal attack has set in. The nasal mucous membrane then becomes so swollen and the secretion is so great that serum can only with difficulty be applied, and is at once washed out by the great flow of watery mucus. Toxin has also entered into the circulation, and into combination with the body cells, enormously increasing the difficulty of serum treatment. In the treatment of such an attack, especially if asthma symptoms be also present, it is recommended that the patient should retire to rooms with doors and windows shut, and remain there until the symptoms have subsided. This will be hastened by using serum locally, at first every 10 minutes, and afterwards at longer intervals. When the attack has passed off, the patient should endeavour by such prophylactic use of the serum as has been described to prevent further attacks from appearing. The use of pollen antitoxin is not followed by any ill-effects, nor does it create a habit. On the contrary longer use imparts a certain slight immunity to the hay-fever poison, rendering the need for frequent applications less.

It was thought possible at first that by the use of subcutaneous injections patients might be passively immunised against hay-fever

toxin, but the results with this method prevented its recommendation. Experiments made by Dunbar and Prausnitz<sup>(10)</sup>, injecting hypodermically 1—2 c.c. of serum, certainly showed a favourable result in lessening the severity of attacks for three or four days. There was found particularly a distinct decrease in the local subjective symptoms, and in the general feeling of malaise. Immunity to the toxin, it is true, was not attained through the relatively small amount of serum used, but natural attacks of the disease, or attacks artificially excited by means of pollen, were in consequence of much less intensity, and more easily allayed by antitoxin locally applied. Similar results were observed by Borrowman<sup>(5)</sup> in two cases where the injections were repeated, in the one case thrice, and in the other four times. Other doctors also in spite of Dunbar's warning appear to have employed this method.

This warning against the use of subcutaneous injections was given, because in most cases there appeared at the site of injection four or six days after, a swelling with erythema and much itching, and often an urticaria-like rash. These appearances usually lasted about a week and then gradually disappeared.

Sir Felix Semon<sup>(22)</sup>, in reference to these after-effects, said, that it was obvious to him that the antitoxin as at present used must still contain toxic or septic properties. When he wrote this he must have been unaware of the strictness of the precautions taken, as previously described, to ensure that no pollen toxin remained undestroyed in the serum, thus preventing the possibility of the serum in use containing toxic properties. Careful testing for sterility in every case also precludes the possibility of the serum's possessing septic properties. When the serum was 'pasteurised,' or exposed to a temperature of 60° C. for half-an-hour, it caused the same effects after subcutaneous injection as serum not so treated. In not one of the many hundred laboratory experiments with local applications did the serum cause the slightest irritation to the mucous membranes of eye or nose. Irritation is occasionally noticed in a few hay-fever patients during the time of its prevalence when serum is applied to the sensitive mucous membrane of the eye in the course of an attack, but this effect is also produced by the application of any other remedy.

Although therefore these after-effects of subcutaneous injection appear to be quite without any dangerous significance and to be similar to those serum exanthemata observed after injecting other sera, *e.g.* diphtheria antitoxin, yet on their account Dunbar felt it inadvisable

to recommend the method. Could these irritating properties be removed the method would be one especially applicable to the treatment of asthma symptoms, but in the meanwhile it is satisfactory to know that local applications of the serum when properly used suffice to keep any patient free from attacks of the disease. A consideration now of the cases will show that the prophylactic use of the serum was followed by most excellent results in a great number of instances. A few found difficulty in the treatment at first, and only got a satisfactory result after obtaining the dried preparation without addition of carbolic acid.

*Results of Serum Treatment in European Hay Fever.*

	Positive results	Partial results	No improvement
	127	71	24
Result in cases complicated with asthma }	14	6	9
Result of serum treatment in %	57 %	32 %	11 %

### Cases.

The cases will now be cited in some detail, and are arranged in the order of the results obtained. The cases of the disease in America have been reserved for a special description at the end.

The total number of patients who during last summer sent reports of their experience with pollen antitoxin amounts to two hundred and eighty-five. The cases are representative, as the patients reside in very different countries, where different forms of the disease might be expected. Reports are to hand, namely, from England, Scotland, Germany, different parts of Austria, France, Holland, Denmark, Russia, Switzerland, Italy, and America.

Excluding reports from the last-mentioned, the communications deal with 222 hay-fever patients. When it is stated that a completely successful result followed the use of the serum in 127 cases representing 57 % of the total, it will be agreed that such a result, considering the difficulties and misunderstandings always present on the first introduction of such a remedy, is both satisfactory and highly encouraging. In 71 cases, that is in 32 %, a partial result was obtained. 24 patients or 11 % were unsuccessful in obtaining any benefit from its use. 171 patients,

which is a majority of the cases, found it relatively easy to keep themselves free from attacks by its means.

*Cases where Complete Results were obtained by Treatment.*

A few typical case-histories will be given in detail.

*Case 1.* Dunbar has already published the case of a young officer, a great sufferer from hay fever which made him dread the manœuvres, when his duty compelled him to be actively employed during the hay-fever period, in the open air amongst flowering cornfields. During last year he had also important work on hand necessitating his being in good health. He was able by using a drop of *fluid* serum every morning before rising, in each eye and nostril, to keep himself free of all irritation for four or five hours at a time, even at the height of the hay-fever season. In the second half of June he was able after using serum on one occasion to keep all attacks in abeyance for nearly two days except that he sneezed six or seven times, in the morning and evening. He said that he had never before come so easily through the hay-fever season.

The following communication from a doctor in Görlitz is given in full.

*Cases 2—11.* "I had the opportunity of treating ten patients with the serum without a single case of failure. I followed the accompanying directions carefully and strictly and obtained a very excellent result in five of the patients, whose eye symptoms were more troublesome than the nasal. In the case of two of these patients (both officers) for several days in succession two drops of serum were instilled into each eye, in the early morning before they went on duty, and they both agreed in reporting immediate relief from the burning in the eyes, and that they were able to take part in exhausting manœuvres in dust and sunshine, which was formerly quite impossible for them. The effect of the serum passed off after twenty-four hours, sometimes earlier: it lasted longer in cool than in hot weather. In the case of the other patients the excessive secretion from the nose and eyes immediately diminished. A lady very sensitive to the hay-fever poison found that the effect of the remedy only lasted a few hours (five to six). With three others it lasted even in sunny weather for three or four days."

The following is the case-history of a lady, in whom the effect of the serum was carefully observed by her family doctor.

*Case 12.* Lady in Stettin, Germany, 30 years of age, is otherwise perfectly healthy. She is in no way hysterical, a woman of sound judgment and reliability. Outside the hay-fever period she is able at all times to fulfil her social and domestic duties. For many years past patient has suffered from hay fever, which, coming on at the end of May, lasts several weeks, during which time she is quite unable to do anything. The conjunctival and nasal irritation is so severe as to cause her much suffering. Three or four years ago the hay fever was so bad that for some time she required to remain in bed on account of diffuse bronchitis, with asthmatic symptoms.



*Experience with the serum.* Fluid serum was used. First attack in 1903 was on May 29th. Between the 3rd and 5th June the conjunctival blood vessels had become intensely injected, and the nasal mucous membrane was red and swollen. After instillation of the serum the patient found subjective alleviation, and the objective signs disappeared. She felt "as though the serum prevented an extension of the process further than the throat."

After three days, during which 2 c.c. serum had been used which had kept her free from attacks, her stock of the antitoxin was exhausted. She felt the want of it very keenly.

Since using the serum she can go out of doors even in the worst days of the hay-fever period, and she maintains that she not only got immediate improvement by its use, but that on those days when she did not use it a certain beneficial after-effect was perceived keeping the illness in check.

*Cases with Positive Result after initial difficulty with the treatment.*

Still more instructive are the case-histories of those patients who experienced at first considerable difficulty in obtaining a satisfactory result through serum treatment, but later on succeeded in protecting themselves from their attacks by its use. This preliminary difficulty is to be explained either by an unusual susceptibility of the individual to the carbolic acid contained in the fluid serum, or probably in most cases by incorrect use of the serum, the patients not carrying out the important directions for prophylactic treatment.

*Case 13.* Doctor, 41 years of age, in Amsterdam.

Has suffered severely from hay fever for 24 years and is usually rendered almost incapable of work from the middle of May till the end of July. He is affected alike in town and country, and has attacks even in the house, where doubtless as he himself says pollen grains are brought in by clothes, newspapers, etc.

In treatment he has not found much benefit from former remedies. He tried without success antifebrin and quinine internally and local applications of adrenalin and cocaine, also treatment by the galvano-cautery.

*Experience with the serum.* His first attack in 1903 was on 25th May at 9.30 a.m. At 10 o'clock he instilled five drops of serum into each nostril, and one or two drops into each eye. Result in three minutes absolutely successful. The effect in the nose lasted till 2.30 p.m., when a fresh nasal attack was aborted by five drops of serum in three minutes. In the course of the next few days he found that instillations once or twice a day sufficed to keep him free from attacks. On the 28th May he required no serum. The eyes were always easier to keep in a normal condition than the nose.

In the beginning of June he found that he obtained no relief from attacks of his hay fever by use of serum. At the same time he was also suffering from an acute attack of rhinitis, and while that lasted the hay-fever attacks were unchecked by the antitoxin, although lessened in severity.

The "cold" passed away with the use of Salipyrin. On the 9th of June patient had a pure attack of hay fever. The day was warm and an east wind was blowing. The cold in the head was by this time gone. On this day cocain was tried, but gave no material benefit. After the use of the antitoxic serum he was in half a minute quite free from symptoms.

Dried serum was sent to patient on the 23rd June. Since then he has been able, by the constant use of this preparation, to keep himself continuously free from all attacks. He wrote repeatedly to say that the dried serum had most excellent results; usually it was only necessary to employ it in the nose, although in severer attacks it was applied to the eyes as well.

*Case 14.* Doctor in Jena, 54 years of age. Has suffered from severe hay fever and asthma since 1867.

At first the irritation is limited to the conjunctiva, then it spreads to the mucous membranes of the nose and deeper air passages, giving rise to asthma. There are also symptoms referable to the stomach and rectum. He suffered so severely in 1870 that marked mental depression supervened. He describes the asthma attacks as being particularly severe, but the condition in the eyes and nose was at times almost unbearable. He noticed that after severe attacks there often followed periods of rest which might possibly be ascribed to active immunisation. Treatment formerly by introducing water into the nose gave him some slight relief. Cocain was not of much help to him. Formalin gave rise to great irritation.

*Experience with the serum.* In 1903 his hay fever began on 28th May, and the first slight attacks were successfully treated by instillation of the antitoxin. On the following days the patient journeyed from South Germany, through the Harz to Heligoland. Several attacks occurred on this journey, which by use of serum were either cut short or improved. On 4th June while climbing the Brocken he had a severe attack. On using serum he noticed that there was marked diminution in the vascular injection of his conjunctivae. This was confirmed by two other doctors.

On the 9th June, on a sailing cruise to Heligoland, he had a severe attack. Another hay-fever patient on board was affected at the same time. Instillation of fluid serum into his eye was followed by immediate improvement. This improvement was less marked in the nose, but the nasal hypersecretion was distinctly lessened. The patient was not, however, able to keep himself continuously free from attacks by means of the fluid serum, and even with the dried serum he was unable at first to successfully combat the disease. On the 19th and 20th, which were hot, windy days, patient was comparatively free from hay fever, although he had slight asthmatic attacks. After the 21st June he found more benefit from the antitoxin. On that day he sniffed powdered serum up the nose, and also introduced some into the eyes. During the day he was exposed to much pollen infection, having to stand for two hours under a hot sun and remain the whole afternoon in the open, and danced in the evening, yet had no attack and passed the next day also without attack, only having a slight increase of nasal secretion until the evening, when a fresh attack was immediately cut short by the powdered serum. On 27th June, when the hay-fever season was still at its height, he wrote that since he decided to sleep with windows closed and use the serum immediately on waking in the mornings he had been quite free from attacks, except on two dry, hot, and windy days, when he had not used the remedy at the proper time.

Besides these cases given in detail, there are communications from eight other patients, all persons of unusual susceptibility to the pollen poison, whose cases illustrate this same initial difficulty and final success from prophylactic use of the serum. An interesting experiment on two of these patients may here be described.

Accompanied by a doctor, not subject to hay fever, a railway journey was made to a place in the neighbourhood of Hamburg, where there was much corn and grass in flower. The day was sunny, with a slight wind. Patient *A* used serum prophylactically and repeated its use on the appearance of the slightest irritation. Patient *B* used no serum. Patient *A* remained continuously free from attack, only requiring to sneeze once during the excursion. Patient *B*, on the other hand, suffered from repeated severe sneezing fits, was incapable of work in the evening, and still felt the effects of hay fever on the following day.

On 24th June the same tour was again made, but this time patient *A* used no serum whereas patient *B* did. On this occasion patient *B* was able to completely protect himself from attacks, as did also another hay-fever patient who took part in the excursion and used serum. Patient *A*, however, suffered on this day from sharp eye and nose attacks, and was in a very miserable condition in the evening.

It is of great importance to know that the pollen antitoxin has been effectual in combating even the severest symptom of hay fever, viz., the asthma attacks. Hay asthma can apparently be excited by the local action of toxin from pollen grains which have reached by deep inhalation the bronchial mucous membrane, or it may arise from toxin absorbed by the mucous membranes of eye and nose and circulating in the blood.

It will be remembered that asthma resulted from a deep inhalation of pollen, in the case of the experiment with a hay-fever patient in the glass chamber. Similar asthma-like attacks resulted in a hay-fever patient from unintentionally breathing in powdered pollen toxin in the laboratory.

Further, it is known from earlier experiments that after subcutaneous injection of an extremely small quantity of pollen toxin asthma resulted, showing that toxin circulating in the blood may excite an attack of asthma. We may therefore suppose that natural hay asthma may, in many cases, result from a toxin absorption from pollen on the nasal mucous membrane. Such a toxin absorption probably explains those general symptoms observed by every hay-fever patient, such as depression and irritability, lassitude, sleeplessness, fever, etc. This points to the necessity in treatment of neutralising the pollen toxin before it can be absorbed into the blood.

*Results in treatment of asthma cases.*

The following histories show the influence of the antitoxin on cases with asthma.

*Case 15.* Postman, 38 years of age, living in the Harz mountains. Suffers from severe hay fever, with bad asthmatic attacks. Since 11th July he used dried serum daily, morning and evening, applied to each nostril and to his conjunctivae. All symptoms disappeared after a week's treatment. The result of treatment was afterwards complete.

*Case 16.* Patient suffers every year, from end of May onwards, from attacks of sneezing, conjunctivitis and tickling sensation in the ears. Attacks in 1903 were at first slight, and were benefited by adrenalin. After a walk in fine weather in the neighbourhood of Vienna amongst meadows a severe attack in eyes and nose appeared, which obstinately continued for several days and nights. At this stage fluid serum was tried. After 1 c.c. had been used all symptoms of asthma and hay fever passed away, and the patient's medical man reported the result as a very successful one.

*Case 17.* Lady, 25 years old. Suffered for several years from severe hay asthma. All possible remedies had been previously unsuccessfully used. Only by resorting to a locality on a higher elevation where grass flowered at a later date could she in former years keep attacks away. Last year energetic treatment with pollen antitoxin was begun, soon after the commencement of the hay-fever attacks. Within a day and a half all symptoms were gone, and the patient remained free of attack, till, after a long bicycling excursion amongst flowering crops, an attack set in, but only of moderate severity, which was soon checked.

Since then patient succeeded in keeping herself free from all attacks without being compelled to keep the house.

Naturally such results with asthma symptoms were not always obtained, and indeed it was very frequently found that hay-fever patients succeeded in checking by use of serum all their symptoms with the exception of the asthma. Such cases belong really to the group of partial results, but a history may be cited here in detail in order to complete the discussion of asthma.

*Case 18.* Middle-aged male patient, has been affected for 15 years, from end of May onwards, with hay fever and severe asthma. By instilling fluid serum twice daily patient could almost completely get rid of his nose symptoms, whereas, in the previous year, he often had to sneeze twenty or thirty times in succession, and suffered from very profuse lachrymation. The asthmatic attacks, however, were about as severe as they had been in the previous year, hindering him from working, and making even the simplest actions, such as eating, getting up out of bed, etc., a task.

The reason for this lack of success is not apparent from the communication. The following table gives statistics with regard to treatment with serum in asthma cases.

*Detailed results of Serum Treatment in Hay Asthma.*

Method of application	Positive result	Partial result	No improvement
Subcutaneous injection	0	0	1
Fluid serum nasal	8	6	5
Dried serum nasal	6	0	3
Total	14	6	9

*Cases where complete benefit was not obtained.*

The last leads to a discussion of the second group, viz., those who obtained only a partial result from treatment with the pollen antitoxin.

Seventy-one cases are reported belonging to this category, that is 32 % of the cases treated.

Agreeing with Lübbert and Prausnitz<sup>(29)</sup> I have arranged all those cases of hay fever in this group:

(a) who reporting success with the treatment sent very incomplete details of their cases,

(b) who gave only a preliminary report of success at the beginning of the season, but sent no further communication,

(c) who obtained a successful result with some of their symptoms, but others were not influenced, *e.g.* eye irritation was allayed but not nasal symptoms, or *vice versâ*, or, as was more frequent, eye and nose attacks were checked but asthma remained,

(d) where light or moderately severe attacks were cut short by serum, but where such result was not obtained in attacks of greater severity.

The first and second classes may indeed contain many perfectly complete results, but could not be so used in statistics, since these statistics are based on results obtained throughout the hay-fever season, and not on the effect of serum on single attacks.

In the next class are found those patients who obtained relief during attack from certain symptoms but not from others. The reports of such cases show that as a rule there was an unsatisfactory lack of system in the method of carrying out the treatment, and very frequently an utter disregard of the prophylactic use of the serum. About 68 % of these patients also only used fluid serum.

The eye symptoms were generally found to yield more easily to treatment than the nasal ones. This is explained by the much greater difficulty found by most patients in correctly applying the serum to the nose.

Two examples, besides the case described when discussing asthma, will suffice as illustration of this class.

*Case 19.* A young doctor in Silesia wrote :

"The serum had always a good influence over the affection in the eyes. After injection of one drop the burning almost immediately diminished, and only returned after some hours. The increased vascular injection was not markedly influenced by its use. The result in regard to the sneezing fits was practically absolutely negative. For a short time, perhaps five or ten minutes, there was felt a pleasant cool sensation with dryness in the nose. Sneezing ceased, but commenced again with undiminished force, and the nasal secretion also came on to the same extent as before.

On the whole I sincerely welcome the serum as an efficient remedy, for even the removal of eye symptoms is a great benefit, and is more than any other remedy has hitherto been able to accomplish."

*Case 20.* A doctor in Holland wrote :

"The itching in the eyes disappears on instillation of pollantin wonderfully quickly. The drop at once gives a pleasant cool feeling in the eye. I have not noticed much effect in the nose. At first the sensation is not unpleasant but the secretion is increased, and on the evening of the first day I candidly felt myself very unhappy. The attacks diminished somewhat in severity after a few days."

The next class of cases with partial result includes those who found relief in slight or moderately severe attacks, but where severe attacks were uninfluenced.

From what has been said in the introduction to this discussion this experience is not to be wondered at, and is generally found in practice with other sera, such as diphtheria or tetanus antitoxin, where severer intoxication from the respective toxins is practically unaffected in treatment with antitoxin. In this case pollen antitoxin has not got the chance of influencing severe attacks, not only on account of the physical difficulties in its application, but also because the toxin is already in the blood stream and has entered into combination with the body cells. The right method of treating such attacks has already been dealt with.

*Case 21.* The following case has already been published in the *Geneeskundige Courant*, 1903, No. 28.

Lady, wife of a doctor. She has regularly suffered from typical hay fever for seven years. In the past year it was associated with asthma. In the hay-fever period she frequently suffers from urticaria on both hands and forearms.

After three weeks' observation the doctor came to the following conclusions :

Slight and moderately severe attacks were always promptly cut short by means of fluid serum. To subdue slight irritation in the eyes or nose, one drop of serum sufficed and effectually checked the development of an attack. Larger doses were

required in attacks of moderate severity. The convulsive sneezing was likewise stopped by instillation of a small quantity of the serum in each nostril.

If after exposure to much pollen infection a severe attack ensued, so that the eyes were inflamed and the nose much swollen, then serum had little influence. Its application was rendered next to impossible by the great amount of watery mucus secretion.

*Case 22.* Another instance is that of a young man, a sufferer from hay fever for years, who had tried without benefit different methods of treatment, recommended from year to year. His family doctor reported that use of the serum was followed by such marked result that the patient thought that he was for ever cured. On a journey to a hilly district severe attacks again appeared on which the serum had no influence, obviously because of the severity of the pollen intoxication.

*Cases where no benefit was obtained by serum treatment.*

The last group contains the cases with entirely negative results. Of these communications four cases have not been included, since from their histories they were manifestly not true cases of hay fever. On the other hand there have been included all those cases who from the manner in which they used the serum could not expect any result to follow. This group contains 24 cases, or 11% of the total.

As it has been said, many of these used the serum in an irrational manner, this was practically demonstrated in an instance where the patient was asked by Dunbar to show how he applied the remedy. He put some powdered serum on the back of his thumb, and approaching it to his nose scattered it to the winds in his effort to sniff it up. Yet he imagined he had applied the preparation properly, and had shown its uselessness in an attack. When a few minutes later serum was really introduced into the nose the symptoms of his attack disappeared.

Other patients used the antitoxin far too seldom. A lady from Dundee wrote that she had thrice used fluid serum in the course of three weeks and could not say that she had noticed any marked result.

Quite a number of patients would not carry out the method recommended for prophylactic treatment, refusing to sleep with windows closed. Hay-fever patients have a feeling in the night of the necessity for fresh air, but sleeping with open windows they do not give the sensitive mucous membranes that period of rest from the influence of pollen toxin which they require. By separating out those cases where according to their statements one of the foregoing reasons can be given in explanation of their failure with the serum, 9.6% can be deducted from this group of negative results, leaving only 1.4% of cases where

no reason for this result can be found. Possibly they would have found, as others did, that the powdered serum was more efficient.

From this review of the treatment of European hay fever with pollen antitoxin last summer, it will be seen how very encouraging the results are, and that they give reason for the belief that when all patients learn for themselves the rational prophylactic use of the serum, and carry out all the precautions necessary in their individual cases, they will be able to pass through the hay-fever period without anxiety.

*Benefit from serum therapy in complicated cases.*

If this is a matter of importance to ordinary hay-fever patients, how much more will physicians welcome a means of warding off hay-fever attacks in patients where they form a serious complication of other conditions. Information is to hand for instance from a doctor who treated successfully with serum a case of hay fever in a markedly neurasthenic subject, and by this means greatly improved the nervous symptoms. A similar result was obtained in the case of a lady with psychical disturbance. Several cases of the beneficial effect of serum in patients with arterio-sclerosis are reported, where the strain of the sneezing fits or asthma attacks was naturally a great danger. Also the following case is of unusual interest in this connection.

*Case 23.* Pastor in the country had formerly catarrhal affection of the apex of the left lung, suffered in summer, 1903, from severe hay-fever symptoms. These symptoms consisted of enormous nasal hypersecretion with marked hyperaemia of the nasal mucous membrane. Nose completely blocked to the passage of air. Severe conjunctivitis, and such general symptoms as malaise, lassitude, slight fever, loss of appetite, and especially important a lighting up of the lung mischief in the left apex (Râles medium, sputum mucopurulent, tubercle bacillus not detected).

Instillation of fluid serum according to directions in eyes and nose.

Improvement in nose very soon after, and the passage of air through the nostrils became once more free. The lung catarrh rapidly healed. Patient did not treat the eyes with serum, but with a solution of cocain and zinc, as he found serum in the eyes unpleasant.

*Results in America.*

Attention will now be turned to the experience with serum treatment of hay fever in America. It has been already mentioned in discussing the etiology of the disease that hay fever occurs in America in two forms, viz. 'Spring cold' and 'Autumn catarrh,' and that the



latter differs from European hay fever only in so far as it is excited by the pollen of *Solidago* and *Ambrosia* instead of by grass pollen.

For this reason and from the fact that in consequence of experience already gained the results of treatment were there much better than in Europe, these American cases have been reserved for a special description.

A case of June cold, however, with asthma attacks, reported with successful result of serum treatment (dried serum) from St Louis, U.S.A., has been included in the previous statistics.

The experience of several American doctors with autumn catarrh has already been published. The first antitoxin sent to America was the European antitoxin obtained from rye and maize pollen, but later a special antitoxin was used, which was obtained after the injection of *Solidago* pollen into horses. This latter antitoxic serum could, it was found, be standardised by Dunbar, since his conjunctiva is also highly sensitive to *Solidago* toxin. Reports did not however show that this latter antitoxin possessed any marked advantage over the other.

MacCoy<sup>(17)</sup> of Philadelphia describes his experience with fifteen cases of autumnal catarrh. One of these will here be cited in detail:

*Case 24.* "Patrick — has had hay fever for eight years, coming on in early August. Has not missed a season during the period. The patient has been under my care for six years, and has been treated each year according to the latest and best remedies, but with little relief. Owing to my absence from home during August the patient did not come under treatment until September 2nd. I found him suffering from a pronounced attack. After two days' treatment he had some relief from symptoms. The relief continued and increased, and at the end of the week all symptoms had abated, and he had complete freedom from sneezing, itching and watery discharge, and has no asthma, which in previous years had been especially bad, on or about September 10th. In previous seasons, the asthmatic seizures had been severe, and had lasted all through September and part of October. This case has been under daily observation, and has continued—and remains—absolutely free from every symptom. This patient used eight bottles of serum—about a bottle a day; much more than any other patient under my care."

He further says: "We have all heretofore experienced such deep disappointment in our trials of various methods of cure—surgical and medicinal—that the writer was, to say the least, not enthusiastic concerning results, but he can truthfully say that he believes that no such advances have ever yet been made in the treatment of hay fever."

The total number of American cases reported is 63. Although it may not seem a large number, yet since many doctors had each several cases (10—15 patients) the conditions of observation were more favourable. A large proportion of patients with asthma symptoms were successful in combating it through the serum, as will be seen in the

accompanying table. Such being of greater interest than others the review of cases will be closed by giving in detail the experience of two of them:

*Case 25.* Patient living in St Paul, Minn., U.S.A., suffers every year from end of May till end of September from severe hay fever, with asthma and loss of sleep. After this she is much prostrated and requires a lengthened stay at a health resort before she is well again. In 1903 the first appearances of hay fever began on 21st July. From 15th August onwards she used pollen antitoxin with strict regard to the instructions. Within a week she was completely free of asthma, and was able to stop treatment on 12th September.

*Case 26.* The last case is that of a patient who has suffered for a number of years so severely from hay fever that she required to keep her bed for the better part of six weeks. In 1903 serum came into use on the day following the appearance of the first symptoms, on the 18th August. By its use the patient was able to pursue her usual duties without discomfort and had very little asthma. She was able to leave off treatment after three weeks.

The general results and percentages of recovery after serum treatment in autumnal catarrh are given in the table below. It will be seen how satisfactory and promising they are. It is needless again to enter into a discussion of the partially positive and negative cases.

The same considerations apply to them as did in the case of our own hay fever, and it is to be hopefully expected that in this year the number of such results will, with a better understanding of the exciting cause of the disease, greatly diminish.

*Results of Serum Treatment in Autumnal Catarrh.*

	Positive result	Partial result	Negative
Cases complicated with asthma	44	12	7
Result of serum treatment in %	8	2	3
	70 %	19 %	11 %

*Conclusions.*

In conclusion, briefly summarising the chief points discussed in this paper, it will be noted that Dunbar has, by his researches, gone very far to prove that there is in reality but one exciting cause for hay fever, this being the pollen of grasses and of certain other plants. He found that these pollens could artificially excite attacks of hay fever when applied to the conjunctivae or nasal mucous membranes of persons predisposed to the disease, and this even outside of the hay-fever

period. The attacks were in every way similar to attacks of the natural disease. Dunbar tested all the theories previously advanced to explain the etiology of hay fever, but found them all unsatisfactory. He succeeded in isolating the peculiar poison in the toxic pollen, and found it to be an albuminous substance, so toxic that even 000025 milligrammes of the proteid body, consisting of this active albumin and also of inert globulin, could excite irritation in the conjunctiva of a predisposed patient. This amount of toxin would be contained in two or three pollen grains. Large doses produced very severe attacks, and toxin injected subcutaneously produced most unpleasant and indeed dangerous symptoms in two hay-fever patients. Yet potent though this toxin be in exciting hay-fever-like attacks in subjects predisposed to the affection it is absolutely without any effect on normal persons.

By injecting pollen toxin into animals Dunbar succeeded in obtaining an antitoxin, which neutralised the toxin *in vitro*, and cut short attacks of hay fever artificially produced by the toxin. Furthermore the antitoxin cut short attacks of the natural disease. The toxin and antitoxin have been tested by a large number of doctors and patients in different parts of the world, with results which confirm Dunbar's. The antitoxin appears to be quite harmless. Owing to the peculiar nature of the disease, and the constant reinfection of the mucous membranes by pollen on exposure in the outside air, Dunbar has found it to be necessary, in treatment, to use the serum prophylactically, to sleep with windows closed, apply serum in the morning before rising, both to eyes and nose, and again during the day on the appearance of the slightest irritation in the conjunctiva or nasal mucous membrane. By this means he has succeeded and others have also been successful in keeping absolutely free from attacks of the disease.

It is to be hoped that the value of antitoxic serum treatment will be yet more widely tested in the coming hay-fever period, and the results carefully recorded, in order that statistics drawn from a very large number of cases may be obtained and the question of hay-fever etiology and therapeutics be set upon a still surer foundation.

My best thanks are due to Professor Dunbar for his kindness in putting at my disposal the material from which this discussion and review of the recent researches in hay fever has been derived. I have also great pleasure in acknowledging my indebtedness to Dr Lübbert and Dr Prausnitz of the Hygienic Institute in Hamburg for much kind help in the work.

## APPENDIX.

## TABLE OF PLANTS.

*Examined and tested on Hay Fever Patients by Drs Dunbar and Prausnitz for toxicity of Pollen, including all which have been up to the present found toxic. (Collected and arranged by Dr Kammann according to the Linnæan Classification.)*

Class	Order	Specification of Plants	Toxicity of Pollen	Class	Order	Specification of Plants	Toxicity of Pollen
I.		No plants obtainable		V.	1.	Verbascum nigrum	-
II.	1.	Syringa vulgaris	-			Convolvulus arvensis	-
III.	1.	Iris germanica	-			Viola tricolor	-
	2.	Secale cereale	+			Campanula rapunculoidea	-
		Avena sativa	+			Verbascum phlomoides	-
		Hordeum sativum	+		2.	Heracleum sphondylium	-
		Avena flavescens	+			Coriandrum sativum	-
		Oryza sativa	+			Daucus carota	-
		Calamagrostis lanceolata	+			Conium maculatum	-
		Calamagrostis montana	+		3.	Sambucus nigra	-
		Calamagrostis Halleriana	+		5.	Linum usitatissimum	-
		Dactylis glomerata	+	VI.	1.	Lilium Harrisii	-
		Poa pratensis	+			Tulipa	-
		Anthoxanthum odoratum	+			Narcissus	-
		Eriophorum vaginatum	+			Hyacinthus	-
		Cynosurus cristatus	+			Convallaria majalis	+
		Phalaris arundinacea	+			Polygonatum multiflorum	+
		Lolium perenne	+			Scilla	-
		Holcus lanatus	+			Luzula pilosa	-
		Alopecurus pratensis	+		3.	Rumex hydrolapathum	-
		Aira caespitosa	+	VIII.	1.	Oenothera biennis	-
		Brachypodium sylvaticum	+			Erica	-
		Agropyrum repens	+	XII.	1.	Prunus avium	-
		Festuca elatior	+			Philadelphus coronarius	-
		Festuca gigantea	+		2.	Pyrus japonica	-
		Crocus	-			Spiraea ulmaria	-
		Triticum sativum	+		3.	Geum rivale	-
IV.	1.	Plantago lanceolata	-			Rosa (7 different var.)	-
		Plantago media	-			Rosa canina	-
		Scabiosa columbaria	-			Rubus fruticosus	-
V.	1.	Solanum dulcamara	-	XIII.	1.	Papaver rhoeas	-
		Atropa belladonna	-			Tilia platyphyllos	-
		Nicotiana rustica	-			Papaver orientale	-
					2.	Paeonia peregrina	-
						Aconitum napellus	-

Class	Order	Specification of Plants	Toxicity of Pollen	Class	Order	Specification of Plants	Toxicity of Pollen		
XIII.	3.	Trollius europaeus	-	XIX.	2.	Arnica montana	-		
		Ranunculus auricomus	-			Matricaria chamomilla	-		
		Anemone pulsatilla	-			Achillea millefolium	-		
XIV.	2.	Anemone sylvestris	-			Artemisia absinthium	-		
		Digitalis purpurea	-			Artemisia vulgaris	-		
		XV.	2.			Arabis arenosa	-	Centaura cyanus	-
XVI.	2.	Brassica Napus	+		4.	Calendula officinalis	-		
		Geranium sylvaticum	-			XXI.	1.	Euphorbia Gerardiana	+
		Geranium pratense	-					3.	Zea Mays
XVII.	4.	Lavatera thuringiaca	-			Carex vulgaris	+		
		Malva sylvestris	-			Carex intermedia	+		
		Malva alcea	-			Carex arenaria	+		
		Althaea rosea	-			Carex paniculata	+		
XVIII.	4.	Althaea ficifolia	-			Carex glauca	+		
		Cytisus laburnum	-			Carex alba	+		
XIX.	1.	Hypericum quadrangulum	-			Carex verna	+		
		Arcetium lappa	-			4.	Urtica dioica	-	
		Carduus acanthoides	+			5.	Ambrosia trifida	+	
		Leucanthemum vulgare	-				Xanthium macrocarpum	-	
		Solidago odora	+			XXII.	2.	Salix	-
Solidago nemoralis	+	XXIV.	1.	Lycopodium clavatum	-				

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