The proteid contained in the pollen of grasses is responsible for the European hay fever, that in the pollen of rag weed for our autumnal catarrh. The common form of so-called vaso-motor rhinitis, which is induced by the emanations from certain animals, particularly the horse, is evidently of a similar nature, and in this connection it appears to be established that persons liable to this disease are also especially liable to a disturbance of the nature of an anaphylactic shock after the injection of diphtheria antitoxin or other preparation of horse serum. We see also other varieties of vaso-motor rhinitis in which it is not possible to trace the source of irritation, but which lead us to suspect a similar cause. It is possible that in certain forms of chronic infection, especially of the nasal accessory sinuses, a micro-organism is present which produces a toxic proteid capable of acting on the mucous membranes of the nose and bronchi in a manner similar to the toxic proteids contained in pollen or animal emanations. In such a case the patient would be harboring his own irritant and the absence of an external exciting cause would be explained.

There are several questions connected with these cases which need better answers than they have hitherto received. What is the relation between the nasal symptoms and the asthma which so often accompanies it. Is the asthma due to a nervous reflex from the nose or is it the result of the direct action of the irritant on the bronchi; or is it caused by the absorption of some substance acting through the general circulation? Nasal irritation appears sometimes to excite asthmatic symptoms, but it generally does not do so. Concerning what is sometimes called nasal asthma or asthma of nasal origin, I doubt whether such a thing exists, except in connection with vaso-motor rhinitis. In answering the question whether in a certain case of asthma the nose is at fault, a history or symptoms of vaso-motor rhinitis is to be sought and not anatomical peculiarities in the nose.

May not the presence of bilateral polypi in cases of asthma be looked upon as *prima facie* evidence of vaso-motor rhinitis? Chronic vaso-motor rhinitis, asthma and bilateral polypoid formation of the mucous membrane of the ethmoid occur frequently together. In this symptom-complex the relative intensity of the nasal irritability, the asthma, and the polypi varies in different cases, but they are found so frequently together that one cause must be sought for to explain the combination.

An explanation is also needed for the sensitive spots in the nose, the mechanical irritation of which in a person suffering from hay fever brings on increased reflex symptoms, and cauterization of which is often recommended for treatment.

For the laryngologist the question of the etiology of these disturbances is especially interesting if it can suggest a successful and logical

method of treatment. A curious fact in vaso-motor rhinitis is that many cases are relieved of their symptoms by methods of treatment which would seem to be entirely illogical, whatever our theory of the etiology may be, whereas in other cases the same treatment produces no effect. Septal and turbinate operations, cauterizing with chemicals or heat, inhalations and internal drugs appear to produce undoubted good results in some cases and to fail in others. This may be partially explained by supposing that any stimulation of the intranasal structures may in certain cases alter the conditions which make the symptoms possible. Recently different preparations from the exciting pollens have been introduced with the object of rousing a tolerance, but these also do not seem to be final. If all the symptoms connected with hay fever are primarily caused by an intricate biochemical reaction we may hope that logical and effective means will be found to neutralize this reaction. And the possibility is also suggested that the treatment of asthma and nasal polypi may follow in the same direction.

THE ETIOLOGY OF HAY FEVER.*

BY THEOBALD SMITH, M.D., BOSTON.

THE disease known as hay fever is due to pollen grains. That was definitely decided many years ago by English physicians, and it was without knowledge of their work that Dunbar took up the subject anew in 1902. He himself was a victim of hay fever and his assistant, Prausnitz, who did much work with him, and has recently written several papers on the subject, was also a victim of this peculiar disease.

Dunbar first took up the etiology. He was soon led to suspect pollen, and he made a number of experiments which indicated that pollen from the grasses produces the June fever, and it also can be made to produce the same peculiar symptoms when pollen grains are blown into the eyes of susceptible individuals. These observers have used the eye almost wholly as the organ of reaction to determine the effect of the toxins and the antitoxins which they produce. Dunbar soon came to the conclusion that it was necessary to find what precise constituent of the pollen grains was the irritating one. He found that the smooth pollen grains were more concerned in producing the reaction than the fine spiny ones, thus eliminating mechanical activity as a cause. He had pollen grains analyzed, after collecting large quantities of them, especially from the grasses; these were dried and ground up and extracted in various ways. He took out the fats with alcohol and ether and then made a salt solution of the proteids remaining. He also tested the carbohydrates in the pollen grains, which he thought at first might be the active

* Substance of a Discussion on Hay Fever before the New England Otological and Laryngological Society, November 26, 1912.

agent. But on testing the purified carbohydrate he found it negative. In the salt solution extract he found albumin, pseudoglobulin and euglobulin. He purified this substance, but found it best to use the salt solution of the combined proteids. When this was instilled into the eye of a sensitive person he obtained very soon after, the characteristic reactions, which consisted of reddening of the conjunctiva, etc. By using the toxin he was able to make a distinction between the false and true hay fever cases, *i.e.* when the minimum reaction dose was instilled into the eyes of those who had other affections, but did not have hay fever, he found that no reaction took place; he could thus eliminate psychic influences.

He next started to make an antitoxin by using horses for this purpose. He injected them repeatedly with the salt solution extracts. After several months the serum of the horses was tested. He found that in his own eye and that of his assistant he could get the reaction. He first obtained the minimum reaction dose of the toxin by using his own eyes and those of his assistant. He then added the immune horse serum to the toxin and by trying different mixtures of toxin and antitoxin he found the final strength of his antitoxins. For instance, if a given quantity of antitoxin in a 1-30 dilution kept the attack from coming on, when mixed with the minimum dose of toxin which still produced a reaction, he considered it had a strength of 30. In this way he standardized his serum.

Some of these experiments indicated that the systemic attacks are due to the direct inhalation of the pollen powder. In one case, the assistant, who was very sensitive to the toxin, drew into his air tubes a certain amount of the powder and soon afterwards had a severe attack of coughing with dyspnea.

In 1905, after the thousand (more exactly, 997) cases had been treated, one of his assistants collated the data on hand contained in these cases, and it was found that about 60% came out very well under the treatment with the antitoxin; 24% were partially benefited; 16% not at all. The results from these thousand cases were thus very reassuring.

Dunbar maintains the doctrine or hypothesis, that he has to do with a soluble toxin. Such substances, when injected into an animal body, produce an antitoxin. By mixing the toxin and antitoxin, he showed that the toxic effect was eliminated, which indicated that he had to do with a true toxin which could be neutralized by an antitoxin.

Now, in recent years, since the development of our knowledge of anaphylaxis, many observers have considered hay fever an anaphylactic reaction. Let us look for a moment at this reaction and see how it resembles and differs from toxic action. We know that we can rapidly accustom animals to increasing doses of true toxin. Horses can be so immunized as to stand many

thousand times the initial fatal dose of tetanus toxin. The same is true of diphtheria and other toxins. When an animal receives a very minute dose of some animal or vegetable proteid and some weeks later a large dose of the same, harmless to a fresh control animal, it exhibits a group of symptoms which come on very quickly and may lead to death. Thus the guinea-pig which received an excessively minute dose of horse serum two weeks previously, will die if 5 cc. of the same serum is injected subcutaneously, or much less into the peritoneal cavity, or as little as 0.1 c.c. intravenously. It cannot be immunized to this horse serum. It may become temporarily refractory after recovery from the anaphylactic shock, but it becomes susceptible again. There seems to be, therefore, a fundamental difference between toxin immunity and protein susceptibility or anaphylaxis. Both are immune reactions, but the latter is dangerous to the subject.

The current explanation of the anaphylactic shock is as follows: The original injection of proteid leads to the formation of an immune body (anaphylactic-reaction body) which, with the aid of the normal complement of the blood tends, on a second injection of the same proteid, to disintegrate it,—digest it, in other words,—for subsequent reassimilation. One or the other of the component parts into which the proteid is disintegrated may be toxic to the organism and produce the train of symptoms called anaphylactic shock.

The difference between a toxic and an anaphylactic or allergic action (as von Pirquet has called it) is then fundamental. The toxin and antitoxin combine to form an inert substance. The proteid (antigen) is acted upon by an immune body (anaphylactic reaction body) plus complement, and is disintegrated into fragments, one or more of which may be toxic and act as toxins before further disintegration has made them harmless.

In the guinea-pig receiving horse serum a second time in adequate dose, some toxic substance is set free, which acts upon the plain muscle fibre of the body. In the lungs it causes spasm of the muscular coat of the bronchi so that air cannot pass out or in, and the guinea-pig dies of asphyxiation. The lungs are found greatly inflated and this inflation in the guinea-pig is taken as a reliable indication of true anaphylaxis.

The sudden onset of the symptoms of hay fever after instilling the pollen extract or inhaling pollen powder has led the majority of writers recently to interpret the paroxysms as an anaphylactic reaction. Especially the asthmatic symptoms are suggestive. We are far from being in a position to settle this question at present. I can only give a few of the arguments which have been presented.

In the first place, Dunbar's claim to have produced an antitoxic serum which seems well sub-

stantiated, militates against the view that anaphylaxis is dominant in hay fever. On the other hand, the rapidity of onset and the apparent incapacity of the affected person to become immunized, speaks for anaphylaxis. The reaction in the conjunctiva may be called out almost every hour and the attacks last six or seven weeks, or until the pollen disappears from the air. But we know of toxins now which act within one or two hours after injection and we know that immunity to bacterial action may not be durable enough to last from one year to another.

Another line of argument favoring a toxic action in hay fever is the absence of a refractory state in the individual. The individual (man or animal) treated with a proteid in large doses, becomes insusceptible or refractory for a time. It seems as if the immune body (anaphylactic body) had been used up for the time being. In hay fever, no refractory state has been observed either in the spontaneous or experimental cases. The individual remains sensitive throughout the season, and from hour to hour. Experimentally, Dunbar has been unable to produce passive anaphylaxis by transferring serum of the treated horses to guinea-pigs and injecting the protein. In true hypersensitiveness or anaphylaxis, a shock would result under this condition.

Now, there is another way of attacking the problem, by attempting to actively immunize patients who are subject to hay fever. The serum, of course, only passively immunizes them, protects them only for a certain length of time, but if we can inject the pollen toxin subcutaneously and produce such a condition as is produced in the horse for the production of the horse pollantin, then, if immunity occurs, we are justified in saying that we have not an anti-phylactic phenomenon to deal with, but a pure and simple sensitiveness to toxins. This method of active immunization or vaccination has been tried in England and in Germany. Only recently an article appeared by M. Neisser on this subject. The pollen toxin is prepared and put into the eye in from 5 to 5,000 reacting doses, the unit being that dose which produces marked hyperemia of the conjunctiva in sensitive persons. By injecting increasing quantities of the toxin subcutaneously into these 14 or 15 cases, they have obtained certain results. Fully one-half of the cases were very much benefited, some slightly, and some not at all. They were, however, careful to make inquiries of a number of other patients that had not been treated and they found that the season, during which the experiments were made, was such that fully one-half had a much easier time than the year before. These results are not entirely free from criticism, for the good results might perhaps have been obtained without the treatment. But Neisser and his co-worker think that they began the treatment a little too late in the season. The patient should be immunized before he is exposed to the pollen grains in the spring of the

year, if it is a June affair. Another time they mean to try immunizing much earlier and see if they cannot get a larger percentage of successful results. These cases are not to be considered actual cures because all of the patients had hay fever, but the paroxysms were much milder and the patients were more comfortable.

From what has been said you will see that it is not quite possible to explain definitely hay fever as an effect of pure toxins on the one hand, or of hypersensitiveness on the other. The latter explanation is the simpler and is currently accepted. We do not, however, know enough of anaphylaxis itself. There are many phenomena at present thrown together as anaphylaxis, which need further analysis. It is also probable that in this disease the two phenomena are so associated that now one, now the other predominates. Pollen protein may contain both hypersensitizing and toxic substances not yet separated from one another.

Clinical Department.

A CASE OF GASTRO-MESENTERIC ILEUS.*

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AND

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THE reason for reporting this case is twofold. First, on account of the difficulty of diagnosis, and second, on account of the unique maldevelopment of the intestinal attachments, which were so striking that it should be added to the literature of the subject.

The case to be cited is that of a boy three years old who was sent to the Massachusetts General Hospital on October 18, 1912. From the mother the following history was obtained.

The child's parents and four other children were living and well, the oldest child being 17 years of age and the youngest a baby of 14 months. When 6 months old the patient had varicella, but otherwise none of the exanthemata. His development had not been unusual and he was apparently a bright child, but never seemed to be quite as strong as the other children as he had always complained of having "stomach-aches." One year previous to entrance he had a more severe attack of abdominal pain accompanied by vomiting, which lasted three or four days, and was relieved by enemata and castor oil, but since then, aside from any attack of diarrhea ten months before, the patient had been free from any intestinal symptoms.

The attack for the treatment of which the patient came to the hospital, began five days before. On the morning of the day of the onset the patient had his breakfast and noonday meal as usual, and apparently was perfectly well. In the afternoon he became feverish and complained of abdominal pain, but did not vomit. He passed a very restless and

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