

## Section of Therapeutics and Pharmacology.

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### Bronchial Asthma in Relation to Climate.

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DURING recent years it has become generally acknowledged that certain cases of asthma are due to hypersensitiveness to certain substances which either occur in the air and act after inhalation, or are present in food-stuffs and act after ingestion of the food. Some of these so-called allergic substances or allergens are known. Cases of asthma due to inhalation of ipecacuanha or emanations of horses, and cases due to ingestion of eggs or strawberries, have been frequently described.

During recent years our knowledge of these matters has been considerably extended by the work of Chandler Walker, Cooke, Coca, Freeman, Frugoni, Widal and others. A survey of the literature might give one the impression that, as a result of these investigations it would now be possible to determine the specific causative agent of attacks in nearly all cases of bronchial asthma. Since the treatment in these cases has to be a specific one, i.e., to consist of subcutaneous injections with small amounts of the specific allergen, this would imply that nearly all cases of asthma and allied diseases can be treated successfully in a specific way. We will investigate how far this really holds good.

The determination of the specific causative agent is nearly always made by applying so-called diagnostic skin tests, two methods of which are in use, viz., the scarification and the intradermal methods.

Under the scarification method small scarifications are made on the forearm of the patient and the material to be tested is applied either in dry form (with a drop of alkaline solution added), or in the form of an extract. If hypersensitiveness to this substance exists, a large wheal will form. This test always gives a positive reaction if a hay-fever patient is tested with the specific pollen. In other cases of hypersensitiveness to known allergens, such as ipecacuanha, strawberries, the action may also be positive, but in many asthmatics it will be found negative.

Therefore, according to our findings, a positive reaction with the scarification method is an indication of hypersensitiveness to the substance which has been applied, but a negative reaction does not prove the reverse.

*Intradermal* tests with extracts of allergens give positive reactions if hypersensitiveness exists, but the reaction is not specific enough, i.e., the finding of a positive reaction is not a proof that the substance tested has any relation at all to the allergic symptoms.

When some years ago my fellow workers and I applied specific skin tests to a considerable number of asthmatics, we were struck by the fact that so very few cases of true specific hypersensitiveness were found. In 100 patients observed, we found two or three really positive cases. On the other hand, application of a number of *intra-dermal* skin tests revealed a fact interesting to us, viz., all our asthmatics showed positive reactions to several allergens (sometimes as many as thirty or more), whereas normal individuals did not. Particularly, we found that more than 90 per cent. of our asthmatics showed a positive skin test with an extract of human dandruff (prepared in a way described elsewhere by us), whereas normals did not. Our conclusion, then, was that practically all our asthmatics showed signs of hypersensitiveness, whereas we were only able to determine the real causative agent of the attacks in a small number of cases.

This induced us to plan experiments to determine the unknown causative agent in the majority of our cases.

Early in the course of this work our attention was drawn to a fact which is known to all physicians, but the importance of which in relation to the ætiology of asthma has not yet been emphasized, viz., that in the majority of the asthmatics the occurrence of attacks is dependent on the locality in which they are residing. It is known that many asthmatics lose their attacks as soon as they come into the mountains, whereas attacks at once reappear on their return to low-lying countries. It is equally well known that most asthmatics are free from attacks as soon as they are taken into a clinic. On further investigation we obtained the impression that, even in our small country, great differences exist between various places with regard to the prevalence of asthma. This impression was confirmed by a research made on one of the islands (Zuid-Beveland) in the south-west part of Holland (Zeeland). We here found a large number of asthma cases among the rural population; in some villages as many as  $\frac{1}{2}$  to 1 per cent. of the whole population suffered from asthma. Since in other parts of Holland no such prevalence of asthma exists, it could be considered as proved that, even in a small, flat country such as Holland, great differences in the occurrence of asthma exist, which was in complete accordance with the impressions obtained by many physicians and by ourselves. This fact proves that the difference of "place," which has to be ascribed to differences in "climate," cannot be due to differences in barometric pressure, temperature, humidity of air, and similar known atmospheric influences, since these factors differ only slightly in the various parts of our country. Hence we concluded, that the causative agent of the attacks, in the majority of the asthmatics in Holland, must be substances present in the air in Holland and other low countries. The presence of these substances, which are presumably of colloidal nature, is due to peculiar conditions of climate. They occur in the air in large amounts in some places (which are "bad" for asthmatics) and are lacking, or almost lacking, in other places which are "good" for asthmatics. The nature of these substances is unknown; they may be indicated by a name frequently in use before Pasteur's time, viz., miasmata. As will be stated later, we have found two substances which may serve as types of allergic substances due to climate.

The miasma theory explains all the known facts. In many places miasmata occur in the air; consequently individuals who belong to the group which easily sensitize, will become hypersensitive to the miasmata. Also, those asthmatics who have been sensitized to other substances will presumably have been sensi-

tized to miasmata as well. This explains why specific and isolated sensitization to *one* allergen is so rare in Holland. It also explains why most of our asthmatics feel much better in one place than in another, and why in Switzerland, above a certain altitude, they have no attacks at all.

In connexion with our theory it is noteworthy to relate, that one of Frugoni's co-workers, Ancona, found an epidemic of asthma in a certain village, near Florence. He noted that the grain in this region was in a very bad condition that year; it had been fermenting and contained a number of parasites, amongst them one particular parasite, *Pediculoides ventricosus*. Ancona found that every man who for a long time had manipulated this grain acquired eczema, urticaria and asthma. The allergic substance present in this grain was due to the presence of the above-mentioned parasite. This fact is important, as it shows that in those cases where an allergic substance is very active, practically *everyone* who comes in contact with it becomes affected with an allergic disease. It is generally accepted that, as a rule, a certain predisposition is needed for an individual to become sensitized. Ancona's cases show that, in the presence of a very active allergen, no predisposition is necessary; our cases in Zeeland presumably form a transition between the ordinary cases of asthma and those of Ancona.

It need not be said that we have tried to find the causative agent of asthma due to climate, the substance being not only of importance for Holland, but also for all low-lying countries, especially those with a moist climate. We have not yet found the principal miasmatic substance, but, on the other hand, we have discovered two substances which may serve as types of the unknown substances of climate.

We observed a year ago, that grain, infected with *mites*, contains substances, due to the presence of the mites, which produce asthmatic attacks in a certain number of asthmatics. We were able to show that these substances also produce allergic symptoms in guinea-pigs and rabbits. If a certain number of guinea-pigs are placed during a certain time daily for three or four hours in a cage, at the bottom of which is put some grain infected with mites (and sterilized so as to exclude a direct action of the living mites), some of the animals will show allergic symptoms on the first contact with the grain and others will not. But if the experiment is continued, those animals which did not show symptoms the first day, will do so after the lapse of some days. The symptoms will gradually increase in intensity, and after some weeks decrease again; one portion of the animals, therefore, seems to have become immunized. But before this happens some of the animals will have died, either in a condition of shock or from some intercurrent illness. We noticed that very young guinea-pigs for the most part manifest symptoms on first contact; older animals usually do so only after prolonged contact. The allergic symptoms mentioned consist of scratching, sneezing, dyspnoea and general malaise. Young rabbits show a peculiar symptom; they stretch their front legs forwards and their hind legs backwards and yawn violently. The peculiar point of interest is, that *all* animals tested up till now (more than forty guinea-pigs and six rabbits) have shown symptoms of "allergic reaction" when treated in this way.

Besides this substance others were tried. Grain infected with common fungi (*Penicillium glaucum* and *Aspergillus fumigatus*) showed a similar, though less distinct and less regular action.

The experiments mentioned are of some importance, since they are made with a material which causes asthma in a number of asthmatics. The first material mentioned is a non-artificial one, since it may be obtained from a

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peasant's granary or a grocery shop. The second material mentioned (grain infected with fungi) can be artificially made. Oatmeal was sterilized, infected with a culture of *Penicillium* or *Aspergillus fumigatus* (the culture being obtained from other grain) and after growth during some weeks was sterilized again, so as to exclude a direct action of the living fungi on the animals.

One of our experimental results, obtained with grain containing mites on an asthmatic peasant, must be mentioned. A Dutch peasant, who *always* shows symptoms of asthma in Holland, and who, in addition to that, gets acute attacks if he comes into contact with grain infected with mites, was taken to Switzerland. At St. Moritz he was completely free from symptoms, for the first time for many years. Inhalation of the dust of grain infected with mites (which for this purpose he had brought from his own granary) produced asthmatic symptoms after eight minutes; these symptoms lasted for twenty-four hours. Three days later the experiment was repeated with the same result in Davos, where by the courtesy of Professor Loewy the experiment could be carried out with such precautions that psychic influences were excluded.

This experiment is a further proof that the beneficial influence which high mountain air exerts on asthmatic symptoms is due to the *absence* of miasmata. As soon as dust which contains allergens is present in mountain air, asthmatics will have the same attacks there as they have in lower countries.

We will now consider how far, on the basis of the theory proposed, the therapy of asthma is possible.

In those few cases in which a specific causative agent of asthmatic attacks is found, specific treatment may be applied, injections being given with very small doses of extracts of the specific allergen and the dose being gradually increased. This point will not be discussed extensively, as we agree with the current opinion about it, with this difference, that we prefer to conduct this treatment with the smallest doses of allergen possible, whereas some other authors try to increase the dose as far as possible, attempting in that way to obtain immunization.

Since, as has been stated above, a specific causative agent for allergic attacks is only forthcoming in 2 or 3 per cent. of our cases, another method of treatment will have to be found for the great majority of patients. In these cases non-specific treatment will have to be applied.

This treatment is based upon the following two facts: (a) If in a case of hypersensitiveness to a certain substance, small quantities of this substance are injected, usually the sensitiveness decreases, but if small quantities of another allergen are injected, the sensitiveness to the first mentioned substance also usually decreases. (b) It is known that the condition of asthmatics and other allergies may undergo considerable alteration if they succumb to infectious diseases. Sometimes the onset of one disease (bronchitis, for example), may render the condition worse, but sometimes on the other hand certain diseases, such as tonsillitis, pneumonia, or even influenza may ameliorate the condition, or even produce a temporary cure. The same thing may happen if a sufferer from an allergic disease is injected with a foreign protein; in certain quantities it may improve the patient's condition, or in other quantities it may make it worse.

The aim of non-specific treatment, then, must be to find a substance which, if injected in a certain quantity into a certain allergic, will produce as much amelioration and as little increase in symptoms as possible.

The statement made above implies that in all cases of non-specific treatment

of allergic diseases great care is necessary in the choice of the right dose. As a rule small doses—if effective at all—will have salutary effects, whereas the larger doses may do harm. Since the sensitiveness of various asthmatics to the same allergens differs very considerably, it is impossible to assign a fixed limit for small or large doses. For the most part the policy to be adopted should be to begin with a dose so small that it will certainly do no harm, and gradually to increase it till the effective and beneficial dose is discovered.

For this reason anti-allergic treatment of asthma and allied conditions is much more difficult than treatment of "ordinary" diseases in which the active dose is known—within certain rather narrow limits. This fact explains why various authors, using certain substances for the treatment of allergic conditions report good results, but usually experience less favourable results if they try one of the substances used by another investigator. Generally the substance to which the investigator is accustomed will yield him the best results. For reasons stated elsewhere, we have for the past three years applied tuberculin injections as a routine treatment in nearly all cases of allergic diseases. We have found that all these patients are sensitive to tuberculin, and we made use of this sensitiveness to obtain a "reaction" with tuberculin, which is very often beneficial. Sometimes we employ injections with milk or sulphur as additional therapeutic measures. Peptone injections, introduced by Dr. Auld, yielded us less favourable results—perhaps for the reasons stated above—than they yielded in Auld's hands.

Of 300 cases treated by us during recent years, about 50 per cent. were beneficially influenced, so that the patients may be considered (and in fact consider themselves) as cured, or almost cured; 15 to 20 per cent. were not influenced at all. In the remainder of the cases there was distinct improvement.

Without dwelling further on this point, I would only draw attention to the fact, that of the 50 per cent. of cases in which there was either no improvement or only partial improvement, a great number belong to the group in which influences of place or of climate play a very predominant part. The question arises, what can be done for those cases?

I have repeatedly called attention to the fact that in many instances a sufferer from an allergic disease will be completely free from attacks as soon as he goes to a place with a different climate, or even if he enters a hospital. This not only holds good for cases of Dutch origin, but also for the majority of cases in England, North Germany, America, and the English and Dutch Colonies. Probably in many other countries the same phenomenon exists, but I have no definite experience of it.

It is almost certain that any patient who manifests this peculiarity, viz., freedom from attacks in a hospital, will also be quite normal and will not show any sign of allergic attacks as soon as he is taken to places higher than 1,500 to 1,800 m. above sea level. But it must at once be stated that a treatment which consists in sending a patient for some months to the mountains will as a rule only end in causing disappointment. Certainly the patient will be much better and will feel like a normal man up in the mountains, but after his return home he will, in a very short time, be in exactly the same state as he was before he went away. In many cases the improvement will not even last till the patient has reached his home; his attacks may recur on the way back. Nor is it certain that the patient's condition will be what it even was before he went away; we have often noticed that, during the first few weeks after return home, the patient's state of health has become even worse than it was before. All

this is quite intelligible. As soon as the allergic patient arrives at a place where the air is free from those allergens which are noxious to him, he will be free from attacks, but he will be by no means cured, so as to have lost his hypersensibility. This hypersensibility, this allergic state, remains unchanged for many months and even for many years, although during all that time no attacks may have occurred. I have seen numerous instances in which hypersensitiveness in such cases appeared to be in no way reduced even after six or ten years. On the other hand, a complete absence of allergens may even set up a temporarily increased hypersensitiveness, as a certain degree of resistance present may become lost owing to the absence of any reaction.

A short residence in a mountain climate, then, will as a rule bring about no change in the patient's condition; it will only give him a temporary respite. If a patient is financially, and also in other ways, independent, there is nothing against his securing a respite from attacks, or even many respites, every year. If, however, he is without independent means, and if a temporary residence in a mountain climate can only be achieved with great difficulty and heavy financial sacrifice, I very firmly dissuade the patient from taking this step. In such cases everything should be done to treat the patient at home, and, as has been discussed above, even taking the patient temporarily into a hospital during this treatment should be avoided. Only in very severe cases, where death is threatening, must there be a departure from this rule; such cases may have to be admitted to hospital or sent to the mountains.

The question, however, assumes quite a different aspect if it is possible for the patient to change his residence *permanently*. For many people this is impossible, but on the other hand there are a certain number of allergics whose health might quite well be improved by a change of residence, if only they knew to what place they should go. A physician who has treated a number of cases of allergy will easily be able to give general indications about places which, as a rule, are "bad," and about others which, as a rule, are "good" for allergics. In every case, however, the patient himself will have to test whether a certain place is really suitable for him. Before taking measures for establishing himself permanently in a certain town, the allergic should temporarily, for some weeks at least, stay in that place, and as close as possible to the house in which he will probably have to live afterwards, in order to test whether he is indeed free from attacks there or not.

One important point relative to the choice of a permanent dwelling-place should be mentioned. The patient must choose a place which is just at the limit at which he is able to live in comfort. If, for example, a patient knows that he is quite free from attacks at a level of about 1,500 m., it would be very unwise to choose as a permanent or temporary residence a place at 1,800 m. for the following reason: Allergenic substances are never completely absent from the air; there are more of these substances at lower levels and less in the mountains, but they are never completely absent. Now we have seen that a complete lack of allergen in the air may lead to a loss of resistance in the patient. His sole chance of being more or less de-sensitized consists in coming into frequent contact with subliminal doses of the allergen. Hence it will be useful for him to choose a place not much above the level of his tolerance; this will enable him to inhale his allergen daily in small subliminal amounts and may tend to increase his resistance.

Has a permanent residence in the mountains to be really *permanent*? In many instances this is certainly the case. I have seen people who had lived in some asthma-free place in California for ten years and more, and who

succumbed to attacks almost the same day that they arrived in Holland. We have observed the same thing in children who had been educated at schools in the mountains of Switzerland.

On the other hand it must be admitted that, especially in the case of children, there is the possibility that, after a residence of some years in the mountains, the allergic condition may have passed away. However, when children or adults are sent from home to other climates in order to avoid allergic attacks, all calculations and plans should be made on the supposition that the change will have to be permanent. If, later on, it can be shown that the allergic state has really passed away, this should be considered in the light of a fortunate chance which was not to be anticipated.

Till now I have been speaking of mountain climate, but of course a climate which is salutary for an asthmatic need not always be a mountain climate. Sometimes a seaside or any other climate in which allergens happen to be scarce will do just as well. Even in Holland, where there are no mountains at all, change of residence within the limits of the country will often suffice. Only in very severe cases will mountain climate be indispensable.

It is superfluous to state that the term "allergens" used in this connexion is not a fixed entity. Substances which may be allergic for a sensitive patient born in Holland, need not be allergic for one born in America. Still, it is remarkable that asthmatics from very widely separated countries often agree fairly well as to the places, all over the world, which have to be considered as "bad" or "good." And if climatic factors play any part at all in the case of a certain asthmatic, it may be predicted with almost absolute certainty that mountain air at about 1,500 m. will be of great benefit to him.

#### MOUNTAIN CLIMATE COMBINED WITH ANTI-ALLERGIC TREATMENT.

The statement that change of climate of short duration does not materially improve the patient's condition, need not hold good if the patient is treated anti-allergically during his residence in a mountain climate. This is a point which needs to be emphasized. Physicians in mountain sanatoria should make themselves acquainted with the technique of anti-allergic treatment. If they could give proper treatment there would be a chance of really benefiting the patients.

In a certain respect these physicians are in a difficult position, since their patients do not show attacks in their sanatoria, and consequently it is very difficult for them to judge whether the anti-allergic treatment has gone far enough. In other respects, however, the physician in a mountain sanatorium is in a very favourable position. For those who apply the anti-allergic treatment at home there is always the possibility of injecting too much allergen, since they do not know how much of the, often unknown, allergen will at a certain moment occur in the air. In the mountains this quantity is negligible so that the physician there has much less risk to encounter.

Apart from these considerations there appear to be two other possibilities for the treatment of allergic diseases due to climatic influences. Since only preliminary investigations have been made in this respect, I am not yet in a position to communicate definite results; I only want to mention these possibilities in order to point out in what direction improvement, in the treatment of these severe forms of allergic disease due to climatic factors, may be found.

If it is true that many asthmatics only suffer from their attacks because a substance toxic to them is present in the air of the low-lying countries, it

might be presumed that they would be free from attacks if they stayed in an air-tight room, into which only air could pass which had been filtered, so that all allergic substances were kept out. Filtration of air may be accomplished by passing the air through cotton or through a layer of fluid—glycerol for example. Both methods, and combinations of it, have been tried by us. It is not yet advisable to publish these methods in detail. I will only state that it has been proved that in principle our surmise is correct, i.e., patients suffering from violent attacks of asthma in a certain house may be free from attacks, if they stay in the same house in an air-tight room, ventilated in such a way that only air, free from allergens or miasmata, can enter.

If it is possible to arrest miasmatic substances by filtering the air through cotton, it must be presumed that the cotton used as a filter in the ventilation system of the room above mentioned, should contain the miasmatic substance characteristic for the country in which the experiment is made. Since it is a general rule that injections of small quantities of an extract of a causative agent of allergic attacks ameliorates the condition, whereas larger amounts are noxious, it was to be expected that extracts of the cotton mentioned would act in the same way. This surmise also has proved to be correct. Details of these investigations will be published later.

### Clinical Experience with Powdered Leaves of Digitalis.

By E. COWLES ANDRUS and EDWARD P. CARTER.

To the physician dealing with heart disease it is extremely important that he have digitalis at hand in a form which is at once stable and, in so far as is possible, standardized. With regard to stability there is much to be said in favour of the dried powdered leaf. In this form the preparation retains its potency for a considerable period, whereas the tincture or infusion is known to deteriorate with age.

The pharmacological standardization of digitalis has been the subject of careful study during recent years and various methods of so-called "biological standardization" have been put forward. Into the details of these procedures we need not here enter, but it is sufficient to say that they involve the determination of the amount of some form of extract of the drug required to stop the action of the heart of the cat or frog. Certain features of these methods make them appear unsatisfactory from a clinical point of view. In the first place no process of extraction has been evolved which ensures the complete removal of all the component glucosides. In addition, the evidence is far from conclusive that the elements which arrest the action of the heart of the cat or the frog are those upon which the physician depends for the therapeutic effect in cases of heart failure.

It has, therefore, seemed advisable to attempt a clinical standardization of some form of digitalis. To this end a careful study has been carried out upon a large group of patients in the wards of the Johns Hopkins Hospital, Baltimore, during the past two years. The series was made up of cases of syphilitic, rheumatic and arterio-sclerotic heart disease all exhibiting signs of advanced cardiac insufficiency. It did not include cases of acute cardiac disease. The same details of treatment, apart from digitalis therapy, were carried out in each case, i.e., with regard to rest, limitation of fluid-intake, salt-free or salt-poor diet, and purgation. Morphia was used when indicated.

[April 8, 1924.]