

PROCEEDINGS

COMMUNICATIONS

GESELLSCHAFTSVERHANDLUNGEN

NETHERLANDS SOCIETY OF ALLERGY

Meeting May 8th 1954, Leiden

Symposium: Hayfever

(President: Prof. van Dishoeck)

CLINICAL AND SEROLOGICAL STUDIES IN HAYFEVER

by Prof. Dr. H. A. E. VAN DISHOECK

The clinic for hayfever in Holland and the investigations in this field are discussed. In Holland pollinosis-asthma is not frequent. In children pollinosis does not generally develop before the age of 10. In about 80 percent a combined allergy is present, mostly to inhalants. Positive skin reactions for pollen are found in about $1\frac{1}{2}$ percent of normal people and also in a high percentage of allergic patients, without pollinosis complaints. In bakers and millers sensitive to flour, about 40 percent have a positive pollen reaction, whereas in hayfever patients the flour reaction is relatively seldom met with. Thus the chemical identity of the allergens cannot be the cause. It is suggested that one sensitisation favors the development of another one. Here the disposition of the patient and the exposition to the allergic are of importance. However, the high percentage of flour sensitisation among flour workers of 25 %, increasing with the number of years of employment and with the degree of exposure to flour, indicate that perhaps everybody is liable to acquire a sensitisation, if time and degree of exposure are large enough. Thus the hereditary disposition is surely not the only factor. A sensitisation was found in Dutch people to grasses of Indonesia and visa versa, without any exposure to these grasses. Presumably an identical allergen is present in them.

The chemical properties of the pollen allergen is discussed. Benjamins, van Dishoeck, and German stated that in their opinion the active

principle is a small molecular substance linked to some large molecule. In the ultrafiltrate this principle is present and by adding a protein the activity increases as much as 100 times. Abramson isolated an active body with a molecular weight of 5000 from the concentrate, whereas Rosa Augustin isolated an active body with a molecular weight of 14000 from the filtrate. It has been suggested that in these cases the small active principles are linked to large substances of different molecular weight.

Among other investigations that of de Graaf on passive transfer and of Klein and van Dishoeck on the blocking antibody were discussed. Passive transfer is not possible on an allergic skin and the serum obtained in the hayfever season or during a desensibilisation cannot be used. Activation of passive sensitized skin is possible by direct injection in the skin, by subcutaneous injection. The blocking antibody could be demonstrated not only for pollen but also for other inhalants and also in a case of food allergy. A blocking antibody for housedust could not be demonstrated.

EOSINOPHILIA IN HAYFEVER

by M. G. C. FRANSSEN

The colouring technique and the valuation of Hansel are used. As in normal test-persons some scattered eosinophilic cells are always present, this finding is not significant. However, the finding of groups of eosinophils is always of great importance.

The valuation in percentage from the total amount of leucocytes, gives unreliable results as a large amount of infectious leucocytes will mask a small amount of allergic eosinophils.

In the large amount of secretion obtained from a sinus, the smear technique is unreliable, as the eosinophils may be present only in small quantities. Here a homogenisation of secretion by means of heating for 1 hour to 50° C. and a few minutes of shaking afterwards, is a method for quantitative evaluation of the eosinophilic cells.

The reliability of the nasal eosinophilia as a major allergic symptom has been studied. In 58 patients with demonstrated perennial allergy, 57 presented a nasal eosinophilia. In a test-group of 100 non-allergic persons this symptom was always negative.

About 80 percent of hayfever patients suffer from a combined allergy for other inhalants, and they proved to have a perennial nasal eosinophilia. On the other hand, in 12 pure hayfever patients no nasal

eosinophilia was found outside the season. Thus the absence of nasal eosinophilia outside the season proves that the patient suffers from pure pollinosis, whereas the presence of this symptom outside the season is a strong indication of a combined allergy. In 2 of these patients dry pollen was applied to the nose in winter. After 20 minutes, large numbers of eosinophils were present in the secretion.

As eosinophilia is not present in patients suffering from unspecific, reflectory rhinitis vasomotoria, this symptom can be used to distinguish this condition from an allergic disease.

POLLEN ANALYSIS AND DISTRIBUTION OF POLLEN IN THE NETHERLANDS

by Prof. Dr. F. FLORSCHÜTZ (Velp)

EXAMINATION OF PATIENTS WITH HAY FEVER

by W. J. QUARLES VAN UFFORD, Utrecht

The patient, who will often be able to establish a diagnosis of his own disease, is frequently examined even prior to the hay fever season. In making an examination, the four following points are of special importance:

- a. the inquiry as to complaints in order to establish the diagnosis of hay fever;
- b. determination of the allergic origin of the symptoms, the basis of specific treatment;
- c. the general medical examination, which is especially concerned with contraindications to therapy and unfavourable conditions;
- d. identification of the allergen or allergens, which are the cause of the symptoms. (Not every form of "hay fever" is a hypersensitiveness to grass pollen!).

Sub a. We must inquire after the symptoms of hay fever (whether they remain unchanged or increase—even resulting in asthma—in the course of the pertinent weeks and also in comparison with previous years) and especially accurately establish the period during which these symptoms occur. E.g. any patient, who has symptoms from the end of April until the early part of August, undoubtedly does not show a true hypersensitiveness to grass pollen (since the symptoms of this condition appear during the period from the end of May until the middle of July).

An accurate recording of the history of the patient may be of greatest importance in deciding what method of treatment should be employed. Thus patients who have a fair number of symptoms at night will be ordered to take drugs such as phenergan or benadryl (neobenodine), which have marked hypnotic side-effects, before going to bed, whereas symptoms occurring in the daytime will be treated with other, less hypnotic, antihistaminic drugs. General advice such as to close the windows, to cut the lawns in time, to remove flowers and flowering plants from the house, to take a special diet if necessary (no wheat, no rye), to choose a suitable holiday resort (seaside, moors, mountains) may often be largely based on the patient's history.

It is also essential to inquire after the occupation of the patient. In dealing with a gardener or a florist the fact should be taken into account that his symptoms may be due to pollen with which he comes into contact as a result of his occupational activities. Naturally this contact may also be the result of a hobby (frequent working in one's own garden) or of the fact that the home is in a particular neighbourhood (e.g. situated on an avenue with many lime-trees).

II. *Symptoms of hypersensitiveness.*

1. Residual lesions of previous, more or less severe, allergic diseases.
2. Eosinophilia. An increased eosinophil count of the blood is occasionally also observed outside the hay fever season, while it is particularly marked during this season.
3. During the period in which the symptoms occur the nasal secretions and, in patients with asthma, the sputum, are examined for the presence of eosinophilic cells.
4. Blood pressure.
5. Erythrocyte sedimentation rate. Determination of the erythrocyte sedimentation rate may be regarded as a valuable adjunct. An increased sedimentation rate may be another finding suggesting a chronic sinusitis, which may obscure the clinical picture. It may serve as a warning that possibly there is a disease, to be regarded as a contraindication to specific desensitization. A low erythrocyte sedimentation rate (1 after 1 hour, 2 after 2 hours) is frequently observed in allergic patients and may perhaps be interpreted as a possible symptom of hypersensitiveness.
6. The fact that the patient has one or several markedly positive skin tests (which have not been made with a view to identifying a particular allergen) may be regarded as evidence suggesting that there is a tendency to hypersensitiveness.

When all these symptoms are absent, this raises the question as to whether a tendency toward hypersensitiveness exists in this case (which would imply that not much can be expected from a specific desensitization therapy) or whether there are other diseases, which have suppressed the symptoms of hypersensitiveness.

Pregnancy is no definite contraindication. Careful dosage is essential, however. On the other hand, there is the patient's fear of injections, and her relatives will frequently prevent one from commencing a course of treatment.

When the diagnosis of hay fever has been definitely established from the patient's history and the results of examination, the question arises as to what pollen and possible other allergens the patient is hypersensitive (in Holland spring-time also entails spring-cleaning, i.e. a house-dust period during which hypersensitiveness to house dust, feathers, kapok, etc. frequently increases or becomes apparent) and whether we are concerned with true hypersensitiveness to pollen or whether other factors are also involved, once pollen allergy has opened a wide door. Some impression may be gained from the examination for allergens, positive responses to the skin tests being evidence of a previous, existing or future hypersensitiveness.

- a. no response;
- b. to grass pollen: true hay fever;
- c. only to grass pollen and house dust;
- d. to several pollens and house dust;
- e. extensive hypersensitiveness of the skin.

The data regarding the occupation, environment, etc. of the patient, obtained by recording the history of the subject, will show whether a routine examination is sufficient or whether additional tests should be made.

Another advantage of intracutaneous skin tests is the fact that the intensity of the reaction warns us with regard to the rate at which the injections are to be given during desensitization. A slightly positive test may not be a reason for carelessness, but a markedly positive test must be regarded as a reason for being extremely watchful.

Personal experience:

1. Recording the history of the patient.

So-called constitutional eczema, urticaria and bronchial asthma are frequently observed during the first years of life, whereas this is far less

often the case in patients with hay fever. Hay fever is relatively infrequent in young children. The age at which hay fever sets in is between 16 and 30 in the great majority of cases, while children who constantly play in the grass are much less often affected.

The ultimate cause of the symptoms could not be determined in the majority of the cases. It was no longer known. There are two prominent groups of those who are able to state a cause:

1. The group, in whom the symptoms appeared following sudden contact with an excess of allergens (playing in blooming grass, change of occupation, moving).

2. The group, marked by a temporary deterioration (lowered resistance) of the physical condition. (Infectious disease, examination). In comparison with asthma hormonal conditions are far less often stated to be the cause, either as regards the onset (menarche, climacteric) or with regard to an aggravation or decrease of the symptoms (the symptoms of hay fever frequently remain unchanged during the premenstrual period and during pregnancy).

A positive history of members of the family was known in two-thirds of the cases, the appearance of allergic disease being denied or claimed to be unknown in one-third of the cases.

The hay fever was or had been associated with other allergic diseases in slightly over 50 % of the cases, another reason for not regarding every allergen, which the history of the patient has not shown to be suspect or which yields only a slightly positive response, as an important factor in treatment immediately after the skin tests for hypersensitiveness.

As might be expected, the weather (sun, wind, rain) plays an important part. For some individuals looking into the sun is sufficient to induce a violent attack of sneezing, many long for rain, while wind is experienced as disagreeable. These weather conditions undoubtedly determine the pollen density of the atmosphere and therefore the symptoms of the patient. This also is the reason that many patients are more susceptible out of doors. There is another group, however, showing equally severe symptoms indoors and out or whose symptoms even increase when resting indoors or at night. Patients with vasomotor rhinitis occasionally state that their symptoms may be reduced by exercise (e.g. running). A striking feature is the statement made by a large number of patients, viz. that their symptoms also—though frequently to a lesser degree—occur outside the actual hay fever season. Once the nasal symptoms have appeared, they persist for a longer or

shorter period in a large number of cases, the first night-frost being the latest time limit.

2. Examination for symptoms of hypersensitiveness.

Eosinophilia was observed prior to the hay fever season in 50 % of the cases. The eosinophilia apparently increases during the period in which the symptoms occur.

X-ray examination etc. hardly ever revealed symptoms of sinusitis.

The blood pressure had diminished in about 50 % of the cases.

The erythrocyte sedimentation rate showed a decrease in about one-third of the cases, showing an increase in a somewhat smaller number of cases (in which severe changes were almost always absent).

Skin test: skin tests with grass pollen, and often also those with house dust, are usually markedly positive in patients with hay fever. A positive skin test to grass pollen alone is observed in a fairly small number of cases, while several are positive, though less marked, to others allergens too.

Finally, some data on certain determinations, which undoubtedly are not within the scope of ordinary routine examination.

1. Determination of basal metabolism. As in the case of patients with asthma, about one-third of the subjects showed a moderately increased basal metabolism, usually due to a central cause rather than to an impairment of thyroid function.

2. The marvellous—though unfortunately often merely temporary—results obtained with ACTH and cortisone in the treatment of allergic disease (including hay fever) have frequently raised the question whether the favourable results might be attributable not only to the beneficial effect of the adrenal hormones on the permeability of the capillary walls, but also in part to a diminished function of the adrenals in allergic disease. I was unable to solve this problem in my patients with hay fever. The great majority had normal adrenal function tests as regards Thorn's test (adrenaline) and determination of the total elimination of 17-ketosteroids in 24 hours' urine (determinations by Dr. L. G. Huis in 't Veld). The results are less favourable in patients with bronchial asthma, being virtually identical in patients with other forms of allergic disease.

FIGURE I

Onset of the symptoms of hay fever (100 patients).

A.

0-1 —	1-2 —	2-3 2	3-4 —	4-5 —	5-6 —	6-7 —	7-8 6
8-9 —	9-10 —	10-15 11	16-20 31	21-25 25	26-30 13		
31-40 8	41-50 1	51-60 1	61-70 —	71-80 —	unknown 2		

B.

Conditions claimed by the patients to have resulted in the appearance of the symptoms.

Catching cold	1
Moving	9
Change of occupation	2
Menarche	1
Climacteric	1
Term of military service	1
Examinations	2
General infectious diseases	5
Suddenly, when playing in the grass in fine weather	7
Unknown	71

FIGURE II

*Some data on the history of patients with hay fever.**Period of symptoms*

End of May-middle of July	51 %
End of February-early in March till the end of September ... (usually specified as first night-frost)	10 %
End of May till end of August	19 %
End of May till end of September	17 %
End of May till end of October	3 %

Symptoms

definite in

Increased by sun	18 %
Increased by wind	23 %
Decreased when raining	38 %
Equally severe indoors and out	10 %
Much less frequent indoors than out of doors	8 %

FIGURE III

Some results of examinations for a possible allergic constitution in patients with hay fever (100 cases).

I. Family history + ...	67 %
" " —	33 %
II. Other allergic + ...	52 %
symptoms —	48 %
(revealed by the patient's history)	
III. Eosinophilia of the blood 0-4	48 %
(prior to hay fever season) 4-8	34 %
8 and more	18 %
(Higher percentages are frequently observed during the actual season)	
IV. Blood pressure low	49 %
normal	49 %
high	2 %
V. Erythrocyte sedimentation rate low	29 %
normal	51 %
increased	20 %
(prior to hay fever season)	
VI. X-ray examination of accessory sinuses of the nose: no lesions	93 %
lesions	7 %
(these were always slight lesions)	
VII. Thorn's adrenal function test (adrenaline): + after 2 hours:	55 %
after 4 hours:	24 %
after 6 hours:	4 %
after 8 hours:	3 %
Total number of positive tests:	86 %
(negative) :	14 %
Total elimination of 17-ketosteroids in 24 hours' urine	
(Dr Huis in 't Veld)	
Determined in 60 cases	normal 31 cases
low	22 cases
decreased	7 cases
increased	— cases
VIII. Basal metabolism: normal (— 10 to + 20)	65 %
decreased	4 %
increased	31 %

THE ASPECIFIC THERAPY OF HAY-FEVER

by Prof. Dr. L. B. W. JONGKEES (Amsterdam)

The author gives a description of the non-specific therapeutic procedures one can use in treating allergic diseases of the nose. He especially stresses the point that well indicated operations which do not disturb the internal anatomy of the nose and which do not damage the ciliar epithelium are still necessary if conservative treatment does not give sufficient results. For the use of nose drops it is of the utmost importance to use only those drops which do not disturb the ciliar action as for instance cily substances and concentrated solutions. A 3 % ephedrine or a 1/4000 adrenaline solution may be very effective. A specific and non-specific therapy can only lead to the best results if the allergist and the rhinologist combine their actions in good co-operation. Many local actions may sometimes strongly support the anti-allergic therapy and not only local but also general a specific therapy is often necessary. The allergy often causes complaints only when the body is not in its best condition.

A healthy life with plenty of fresh air, much fruit and vitamins may support other therapies amazingly.

THE SPECIFIC THERAPY OF HAYFEVER

by Dr. J. VAN NIEKERK (Amsterdam)

SOME EXPERIENCES WITH ANTIHISTAMINIC DRUGS IN THE TREATMENT OF HAY FEVER (A report)

by W. J. QUARLES VAN UFFORD, M.D.

Antihistaminic drugs are indicated in the following events:

1. the prevention or suppression of general reactions (urticaria, itching, rhinitis, conjunctivitis, bronchial asthma) during desensitization. In these cases we therefore need an antihistaminic drug with a rapid and powerful action, without too severe side-effects.
2. the prevention or suppression of symptoms of hay fever during the critical period.
 - a. in desensitized patients, who nevertheless show more or less severe symptoms during the first season following desensitization or during unfavourable periods (much sun and wind);
 - b. in non-desensitized patients.

As regards the incidence of the symptoms, the study of the patient's history shows:

1. that they constantly occur and show a constant increase in severity, even taking the form of asthma;
2. only out of doors;
3. only on fine sunny windy days out of doors;
4. only occasionally;
5. only at night.

This determines what antihistaminic drug we shall employ.

We wish the action to be as rapid and as powerful as possible, with no side-effects (drowsiness, gastric disturbances) other than a possible somniferous effect at night. The smaller the dosage, the less often a tablet need be taken (i.e. the more prolonged the action will be), and the cheaper, the better for the patient. Therefore, new drugs, which are claimed better to come up to these requirements, continue to appear on the market.

Now as to some personal experiences:

Sub. 1. the prevention or suppression of reactions during desensitization: satisfactory results were obtained with phenergan, neobenodine and benadryl, histafène, postafène and longifène, pyribenzamine and azaron.

When antihistaminics are given at regular intervals during desensitization, it is advisable not to administer any drugs with somniferous side-effects, as this would be detrimental to the occupational activities of the patient.

Sub. 2. during the hay fever period.

- a. persistent mild symptoms and
- b. constantly increasing symptoms. Continued administration over a period of about 6 weeks is indicated in this case. A powerful action, small dosage, prolonged effect, absence of side-effects and cheapness are particularly essential in these cases.

Longifène, a drug claimed to have few side-effects and a prolonged action as well as a powerful antihistaminic effect, was used during the 1953 hay fever season (of about 200 allergic patients, two showed somnolence and one had vivid dreams; no other complaints were reported). Thirty patients with hay fever were treated with this drug (one group was given 1 tablet of 25 mg. thrice daily after meals, and another group was treated with 2-4 tablets after breakfast, some

patients also being given 1-2 tablets before going to bed). The results obtained were highly satisfactory.

Symptoms of hay fever did not appear in previously desensitized patients and only mild symptoms occurred in those who had not been desensitized.

Satisfactory results were also obtained with longifène in patients already showing allergic reactions to pollen in the early spring of 1954. In addition, one group, comprising patients complaining of severe fatigue, asthenia, apathy, etc., was also treated with another drug, plimasin (a compound of pyribenzamine and a stimulator amine). Administration of pervitin was previously recommended by some authors. Since then the regular (ab)use of stimulator amines has, however, come to be regarded with increasing scepticism. Plimasin was found to be highly effective. It remains to be seen to what extent this treatment also involves the danger of dependence. In any case its use should be considered in patients complaining of fatigue, apathy, etc. and especially in those during examination periods, the drug being administered for a few days prior to and during examination, etc.

Treatment in the other groups will have to be incidental instead of continuous:

administration only in the morning in group b2;

preliminary administration in group b3 only when bad weather increases the chances of severe symptoms and otherwise on appearance of the symptoms;

in group b4 only when symptoms occur and preliminary administration when the appearance even of mild symptoms must be avoided in view of special events (examination, ceremonies, etc.).

Selection of a drug will have to be guided by the physician's own judgment and especially by the individual results obtained in the patient. Every antihistaminic drug will fail in a number of patients, while it will be successful in a number of others. The antihistaminic drug to be used and its dosage should be determined in each individual case. If one drug is known to induce somnolence in a patient and the other does not, then the latter will be the drug chosen if he has to take an examination in the daytime, etc. This will vary with the individual patient. Accordingly, a fixed drug was chosen for continued treatment, the scheme being varied as little as possible, whereas the drug selected for patients with varying symptoms was that most effective and with the smallest number of side-effects in each individual patient, the most suitable dosage being deter-

mined in each case; thus phenergan frequently induces somnolence, there are patients who are not affected by it and others who are only slightly affected by administration of this drug.

In treating the last-named group (symptoms only at night) a fixed drug was chosen, viz. phenergan, the somniferous side-effect of which has a highly beneficial action in a large number of patients. Comparative tests were frequently made between phenergan, a dummy drug, benadryl and neobenodine, pyribenzamine, to be taken before going to bed, phenergan chosen in the majority of cases.

FAILURES IN THE TREATMENT OF HAY FEVER

by P. J. VAN DER WERFF (Amsterdam)

POLLINOSIS IN BELGIUM

by Dr. J. DUCHAINE (Bruxelles)

Dr. Duchaine presents the results of pollen surveys undertaken, from 1949 to 1952, in three Belgian cities, Brussels, Liège and Ostend. The amount of pollen recovered in the atmosphere over the sea-coast is much lower than in the other regions of the country.

As many species, widely cultivated, could have a possible influence on hay-fever in Belgium, the author has specially studied three of these plants: *Hummulus lupulus*, *Beta vulgaris* and *Cannabis sativa*. Skin-tests and history of patients showed that these plants have no importance as hay-fever factors in the country under consideration.

Statistics of tests in 400 patients and the results of specific treatment in 200 individuals have proved that the main cause of hay-fever is due to the pollen of the gramineae; pollen of trees and weeds only play a secondary rôle.

NETHERLANDS SOCIETY OF ALLERGY

Meeting June 19th 1954, Amsterdam

(President: Prof. Prakken)

DRUG ALLERGY

by L. MEYLER, M.D. (Groningen)

The prolonged use of hydrazaline may result in the appearance of a clinical picture marked by joint disease and fever, which bears some resemblance to lupus erythematosus. In addition, a polyserositis was

observed in a number of cases. These symptoms are suggestive of the clinical picture of necrosing arteritis, as seen after treatment with sulphonamide, iodine or thiouracil. Once again, seven of these patients nearly always showed a polyserositis in addition to renal symptoms and polyneuritis.

Preparations obtained from these seven patients were demonstrated and attention was drawn to the following changes in the arteries: necrosis, infiltration of cells in and about the wall of the artery and thrombosis of the arteries. Polyneuritis could be shown to be the result of an insufficient flow of blood through the nutrient arteries, caused by this allergic inflammation. The clinical picture of this form of arteritis bears a resemblance to the changes observed in the phenomenon of Arthus.

Once necrosis of the arteries has occurred, recovery is unlikely. Until necrosis has appeared, recovery may be obtained by timely withdrawal of the harmful drug and possibly by treatment with ACTH and cortisone. The case of a young woman showing severe confusion, lesions of the liver, spleen, kidneys and heart and polyneuritis following administration of sulphonamide was reported. The patient showed a rapid recovery on treatment with ACTH. Conclusive evidence of the fact that the pathological condition was caused by the drug can only be obtained by administering the same drug after the patient has recovered. Experiments of this type, which are not permissible in the opinion of the lecturer, are constantly being reported in the literature. The case of a patient, who had twice taken this experiment himself and who had on each occasion responded with a high temperature, exanthema, polyarthritis, and polyneuritis, is reported, however.

This patient was to have taken sulpharthrol for arthritis, but was given sulphathiazole, owing to a mistake of the chemist. Each time she recovered because she had to vomit, so that medication had to be discontinued. Probably drug allergy is not dangerous in the majority of cases when the drug is withdrawn at the onset of the symptoms. One should watch out for fever, skin eruptions, conjunctivitis, arthritis and a certain restlessness of the patient. Should one fail to withdraw the drug on the appearance of these symptoms, then one will be very liable to induce the clinical picture of polyarteritis. An allergic reaction caused by a drug is believed to affect the blood vessels. Five patients with drug allergy showed transient changes in the electrocardiogram. These changes had to be regarded as evidence of an insufficient supply

of blood to the heart muscle, caused by inflammation or oedema of the coronary artery.

Recently several cases have been reported, in which drug allergy was found to be associated with the presence of LE cells. In view of the resemblance which the clinical picture of severe drug allergy may bear to lupus erythematosus, the present lecturer also carried out investigations to detect this phenomenon. He was indeed able to find symptoms of phagocytosis in eight patients (sulphonamide, arsphenamine, PAS). In his opinion, however, these are not LE cells, but symptoms of phagocytosis, an allied process. When LE cells appear, an amorphous mass is phagocytosed, whereas these cases were marked by phagocytosis of lymphocytes, leucocytes and erythrocytes.

The lecturer proceeded to discuss agranulocytosis, drawing particular attention to agranulocytosis due to pyramidon and the more recent drugs irgapyrine and butazolidine. He personally observed three cases of severe agranulocytosis following the use of these modern anti-rheumatic agents, which were successfully treated with antibiotics and ACTH. Moeschlin's test showed that the blood of these patients contains antibodies, which cause the leucocytes to disappear. Antibodies against thrombocytes were shown to be present in cases of thrombocytopenia due to the use of sedormid or quinidine. In addition, attention was drawn to the many tragic cases of fatal aplastic anaemia following the use of chloromycetin. A particularly striking feature is the number of children of physicians treated with this drug for minor ailments and subsequently dying. In the opinion of the lecturer typhoid fever is the only disease in which treatment with chloramphenicol is indicated. An increasing number of cases of anaphylactic shock due to penicillin is being reported in the literature. More and more patients are being given penicillin and therefore an increasing number subsequently responds by allergy. A curious feature is that the onset of the anaphylactic reaction is very often marked by an unpleasant taste in the mouth. Even anaphylactic shock following local treatment with penicillin (aerosol, eye ointment) has been known to occur. To prevent this penicillin allergy, it is advisable only to use penicillin when definitely indicated. It is not advisable to use penicillin ointment, as the skin is particularly liable to rapidly produce antibodies and as nearly every skin disease can be treated equally well with simple ointments. When subjects, who have previously shown an allergic response to penicillin, require penicillin again, this treatment may be carried out successfully by injecting a small dose of antihistamine (trimeton)

simultaneously with the penicillin. A fair degree of certainty as to whether an individual will show an allergic response to penicillin can be obtained by a simple skin test, which can be read within half an hour.

Finally, allergic reactions induced by vitamin B₁ and insulin were discussed. Arguments were advanced in support of the view, that desensitization is always indicated in insulin allergy. In conclusion, lantern slides from the stomatological clinic in Groningen, showing patients with marked proliferation of the gums, were shown; in some cases proliferation was so severe that the teeth were completely obscured. This proliferation of the gums was observed in patients treated with dilantin.

SOME COMMENTS ON A NEW ASTHMA-THERAPEUTICUM

by W. J. F. v. D. BIJL (Amsterdam)

Since 1950 experiments have been regularly made with a new asthma-therapeuticum (AM-49), in the Netherlands registered under the name of *Resorbiol*.

The preparation consists of a combination of two kinds of pills, AM-49 I and II.

Combination I is a gold-bromide compound dissolving with potassium iodide in the body, from which gold-ions and iodine-ions divide which are supposed to combine with the pituitary albumen and the other heterogene albumina.

Combination II contains arsine acid in order to oppose the concentration of iodine-ions in the thyroid gland.

The combinations of alkali-iodide and particular gold-salts is supposed to bring out an exsudative focus around non-tubercular heterogene albumina, upon which the gold-salts could have their influence.

The system of the glands of internal secretion is supposed to be modified by the therapeuticum in such a way that the production of the adenotrope pituitary hormone is stimulated, while ultimately the remedy would also be effective for psychosomatic patients through the quick improvent of the general condition.

The composition of *Resorbiol* is based on Makiola's research.

Frösch observes in his publication that *Resorbiol* should not be regarded as a wonderful remedy, but that the highest success can only be expected when every patient is treated as a human being in its entirety: in other words if a patient has a psychic trauma, then psychotherapy should be applied first, etc.

Then he gives a survey of 100 patients suffering from bronchial asthma, treated with AM-49 and observed for 3 years. Of those mentioned, 50 per cent recovered within the period of observation; 30 per cent greatly improved, whereas the therapy had no effect in 20 patients.

Rieder also points out that the new therapeuticum has been found to restore a greater number of patients to normal health than any such previously known. Besides he makes the remark that Resorbiol is especially effective in the case of children and persons of an early age.

Ranger strongly recommends a prolonged therapy of at least 7 weeks; while, with a relapse setting in, the cure should be repeated after a few months. She says that the asthma cannot only be fought against by this cure, but that, at the same time, the chance of secondary infection decreases considerably and that the chance of a relapse has also decreased greatly after such an infection. If, contrary to expectation, a relapse should occur, the attack is mostly of a slight character.

She warns, however, against premature stopping of a cure, because in some cases the symptoms might return to a greater extent and because sometimes the therapeutic result occurs *rather late*.

Oehl gives a survey of 23 patients treated by her with AM-49.

She obtains a favourable result with 61 per cent of the cases; dubious 22 per cent; no improvement in 17 per cent.

Steinbacher moreover mentions as a favourable factor the feeling of wellbeing coming almost immediately, and the fact that the patients breathe more easily, so that not only those with an allergic asthma (*a tempo*) recover but the psychosomatic cases can also be favourably influenced by it.

Here is a selection from pertinent literature.

What struck me while reading all the clinical pictures is that there appears to be scarcely any reference to therapy having to be discontinued owing to toxic reactions. Certain precautions should certainly be taken with every case of gold-therapy.

I did not read anything about a contra-indication, e.g. due to diabetes, nephritis, diseases of the liver, colitis ulcerosa, diseases of the blood, dermatitis, lupus, etc.

As toxic reactions to the gold-therapy—and according to the literature, these should occur in $\pm$ 30 per cent of the cases—are described: dermatitis, stomatitis ulcerosa, hepatitis, nephritis, colitis ulcerosa, thrombopeny, agranulocytosis, aplastical anaemia.

Only *Rasscher* indicates in her own case that during the cure

she was treated with Campolen for the "Kräftigung der geschädigten Leber" (strengthening of the damaged liver), but her heart had been damaged a long time before.

As possibilities of reaction she gives latent focuses of infection (granuloma of the root of the tooth, chronic tonsillitis, cholecystitis, pneumonia, myocarditis, nephritis, rheumatism, chronically inflamed mucous membranes of the nasal cavities, of the bronchi, stomach and intestine), but she states that she has never seen severe complications, often these focuses of infection are even eliminated by the therapy.

As all gold-compounds contain ± 30 per cent of gold, the amount administered may become so large that observation is necessary during the cure.

A regular check on blood and urine seems to be desirable in order to be able to administer vitamin-B-complex, vitamin-C, B.A.L. or antihistaminics immediately with the onset of a complication.

1. J. H., a man of 27, is a patient who had shown signs of allergic diseases from his early youth. In consequence of broncho-bacterial damages the illness grew worse gradually. He remained evenly balanced with a constant intravenous ephyllin/Sandoz-therapy only. He was subjected to the cure from the first of September 1953 according to the scheme indicated. After the symptoms had grown considerably worse from the 3rd to the 6th day, he felt a change for the better after 15 days—he slept better and felt inclined to work a little again.

On the 19th of September, I had to discontinue the cure because he had an explosion of acne and an itching dermatitis.

Within four days, the skin-reactions disappeared with vitamin-C injections and antihistaminics, but then he became so oppressed, that the cure with AM-49 was resumed again.

In the week of the 23rd of September to the 30th of September, his asthma improved considerably, but on the 30th of September dermatitis and acne returned.

The doses of AM-49 were continued together with vitamin-C and vitamin-B injections, without any results; after one week, the cure was interrupted again for 10 days.

After that I did not notice any subsidiary symptoms except the acne, his general condition was passable, but from the 23rd of November to the 30th he complained of increasing gastric pains.

The therapy was continued till the 11th of December, but the cure was discontinued on account of his being just as oppressed as previously in the last three years.

2. J. H., a man of 54, has been suffering from bronchial asthma for 40 years, also combined with secondary infections of the bronchial tubes.

In his case, the cure also had to be interrupted after 21 days because of acne and an itching dermatitis. Here the dermatitis also subsided within a week after stopping the remedy, but returned within four days so that the cure was brought to an end, partly because the results were not great.

3. J. M., a man of 19, has had bronchospasmic attacks from his 5th year. There are no bronchiectasies; the heart does not show any defects. Blood-pressure 125/85. About once a week he has an attack lasting 2 to 3 days. The AM-49 therapy gave, after a fortnight, a remarkable improvement of his general condition. He felt much better and all rhonchi had disappeared from the lungs.

Twenty-two days later, viz. on the 36th day of the therapy, he did not feel well, had had no appetite for two days, was tired and on the check-day somewhat short of breath, especially when exerting himself. When after 3 days he had "dyspnoe d'effort" again and a cyanosis with albuminuria occurred, I stopped the therapy.

4. Mr. C., 40 years old, has had asthma trouble for years, and a clear emphysema existed from chronic coughing.

After a week's initial improvement he complained of dizziness, fatigue and heavy perspiration after 16 days, and after that the therapy was discontinued on the 22nd day.

When, on the 29th day, these complaints remained in existence the therapy was resumed and for a fortnight the treatment gave no cause for complaint. He felt that he could breathe more easily, but on the 43rd day, however, he got a tickling cough and palpitations and the asthmatic attacks returned.

Because of his psychic condition, combined with his fear of the new remedy, the therapy had to be stopped without any clearly favourable result on the 55th day.

5. Mr. B., has had occasional attacks of asthma from his youth.

Four years ago he had an ulcer ventriculi, after which no gastric complaints occurred again after a Sippy-cure. The nervous component plays an important part in this case; his asthmatic attacks increased in frequency when one of his children was killed in an accident.

The AM-49 therapy had to be stopped after a week, because he had severe gastric complaints. When the benzdine reaction in the faeces

appeared to be positive I stopped the therapy, although the roentgenologist did not find an ulcer.

6. Mr. T., 39 years old, has had asthma combined with bronchiectasies to a light degree for the last 15 years.

After 12 days, he reacted favourably upon the therapy and could resume his work, but after 21 days the medication had to be stopped because my supply of AM-49 had run out, and because the patient did not possess the necessary means to continue the therapy. Four months later, he had a severe relapse after a bronchopneumonia.

7. P. J., an 11-year-old boy, reacted favourably upon a cure of AM-49 of 5 packages, but after 6 months he had a relapse after an attack of quinsy, though the illness was not so serious as the one he had had before. As this relapse manifested itself only last week, nothing is known about his further reactions upon the therapy.

8. Mr. N., 44 years of age, has also had asthma from his 17th year onwards. Besides the psychic factor, the bronchobacterial component plays some part. He improved considerably through the therapy. After he had felt more oppressed on the 3rd and 4th day, he was in a passable condition from the 6th day onwards, and this improvement continued in such a way that he could even go to a party and kept going until half past three in the morning! From the 21st to the 25th day he developed a head-ache, rhinitis and laryngitis and consequently felt less well in that period, but he need not keep his bed and was able to do his work normally. Previously he was obliged to stay in bed for a few days in similar circumstances.

After 2 months the cure was stopped. The patient had somewhat improved: formerly he had to take three to five tablets of taumasthan a day, but now one or two tablets are sufficient. Up to now he has not had a serious relapse.

9. Lastly, J. G., a youth of 27, who also improved considerably, but was not wholly without complaints even after the use of three packages; but I must admit that the period of treatment was rather short.

Surveying the cases treated by me with AM-49 more closely, I must first take into account that the series of experiments are too limited to express an opinion, besides the duration of treatment of some patients has been rather short, I might say too short. But apart from this, I must say that I have not been so lucky with the Resorbiol-therapy as the literature about it will have it: it says that the percentages of persons

reacting favourably upon the therapy range from 43 to 61 per cent (the manufacturer speaks of "recovering").

In addition, I did see some complications of the gold-therapy in the case of some patients, and thus I shall appreciate it very much when other practitioners will send me their experiences with Resorbiol.

If only we have a sufficient amount of data at our disposal, we are entitled to judge about this newly-imported remedy, the more so because its price is rather high according to our Dutch standards.

SOME RESULTS OBTAINED IN TREATMENT WITH CERTAIN NEW DRUGS

by W. J. QUARLES VAN UFFORD, Utrecht

EFFORTIL

Object: Treatment of chronic symptoms of fatigue and asthenia in allergic patients with hypotension.

Number of patients treated: 25 (mainly patients with bronchial asthma, vasomotor rhinitis and urticaria), treatment with larger and smaller doses being continued over a period of 6-12 weeks.

Results: The symptoms disappeared in 20 cases as a result of, or following, treatment.

No appreciable rise in blood pressure was obtained, however.

HYDROCORTONE ACETATE OINTMENT

Six patients with allergic diseases of the skin were treated.

2 with pollen dermatitis of the face.

2 with constitutional eczema (also affected with asthma).

2 with dermatitis of the hands.

All the patients responded well to treatment, although the constitutional eczema soon recurred.

The ointment was found to be very useful in the event of brief attacks or in the prevention of recurrences.

Attacks (which previously were very severe) could be prevented in the 2 patients with pollen dermatitis.

The ointment is particularly useful in giving the patients the feeling that they can be well at any time, so that the benefit is especially marked from the mental point of view. The question has been asked

whether it might not be possible to temporarily relieve children or adults with constitutional eczema of their symptoms, so that they can be vaccinated against smallpox without the risk of a generalized vaccina.

LONGIFENE

An antihistaminic drug, claimed to have a prolonged effect, a powerful action and no side-effects.

Dosage employed: 1-4 tablets after breakfast and 1 tablet after other meals, and 1-2 tablets before going to bed, if required.

Bronchial asthma.

12 patients with chronic asthma: moderate results.

12 patients with nocturnal attacks (given alternately with calcium tablets and phenergan): moderate results, phenergan much more effective.

12 patients with asthma caused by dust, kapok, etc. (preventive treatment): moderate.

Urticaria.

12 patients with chronic urticaria (slowly decreasing dosage)

7 patients: good.

3 patients: moderate.

2 patients: nil.

Vasomotor rhinitis (6 patients).

5 patients: good.

1 patient: moderate.

Hay fever (30 patients).

(One group 1 tablet thrice daily after meals, one group 2-4 tablets after breakfast and 1-2 tablets before going to bed).

Results: very good (slight reactions in non-desensitized patients in some cases).

Allergic eczema.

12 patients, treated with ointment and tablets.

Results: moderate—poor.

Larger dose occasionally useful in the event of severely itching areas.

The drug was used in a large number of cases to prevent reactions liable to occur during desensitizing treatment or treatment with ACTH and antibiotics. The fact that no reactions occur does not prove that the drug has been effective.

Tolerance.

Administered to about 250 patients.

Somnolence in 2 cases.

Vivid dreams in 1 case.

NETHERLANDS SOCIETY OF ALLERGY

Meeting November 6th 1954, Utrecht

(President: Prof. van Dishoeck)

TREATMENT OF ASTHMATIC BRONCHITIS WITH DRUGS, ADMINISTERED AS AN AEROSOL. THE PROFIT OF PNEUMOTACHO- GRAPHY IN JUDGING ITS MERITS. TRYPSIN A POWERFUL NEW DRUG

by J. C. GERRITS, consulting physician for diseases of the lungs
and O. G. MUNTINGHE, M.D.

Nowadays spirometric examination of functional impairment of the lungs is often undertaken in cases of asthmatic bronchitis and emphysema. They clearly show us the degree of bronchospasm. Especially the figures that connect ventilation with time are of importance. For it makes a great difference when the vital capacity (V.C.) can be exhaled in a normal time or when it requires much longer time. The amount of air expired in the first second of a deep and fast expiration (V_1) is of great importance, as well as the maximum breathing capacity. They are regularly estimated in spirometric examinations.

Windemuller (1) proved that the expiratory curve, when expiring fast and deeply, is a constant curve in each patient and is a hyperbole.

The hyperbolic shape of the expiratory curve can be expressed in a formula

$$C = t \cdot \frac{V_m - V_t}{V_t}$$

C = constant

t = time in seconds

V_m = volume in liters the patient can expire in infinite seconds

V_t = » » » » » » » » t »

Now $K = C V_m$ K marks tardiness of expiration

As a result of this interesting phenomenon one can easily estimate the velocity of expiration at each point of the expiratory phase.

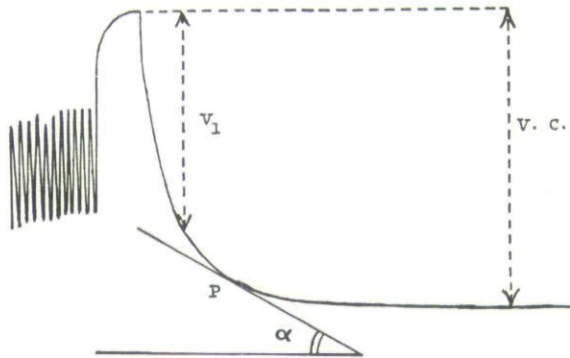


Fig. 1.

This velocity is, for example, at the point P of the curve, equal to the tangent of the angle α . The legs of this angle are formed by the horizontal axis of the hyperbole and the tangent at point P of the hyperbole. *Windemuller* in this way proved that the velocity of the expiratory air is much more important than the vital capacity. This proved to be much more conclusive for estimating the degree of airway obstruction.

However this spiographic method of estimating the velocity of expiration is time-consuming. So pneumotachography has called attention more and more in the last few years, as in this way we can estimate directly the expiratory air velocity. In addition it has the advantage that the apparatus works very fast. So the velocity of the expiratory air is also estimated more exactly.

The whole literature about pneumotachography will not be reviewed

here, but it may be mentioned that it was first described by *Fleisch* (2) in the year 1925. For clinical purposes *Hadorn* (3) modified it in 1942, and we used it in the modification later described by *Wysz* (4) and *Roth* (5). In this apparatus, only the maximal value of the pneumotachographically recorded air velocity is noted in liters to the second. The resistance of the air is low, only 1 cm water; so we can accept that the measured air velocity is equal to the actual expiratory air velocity with open mouth.

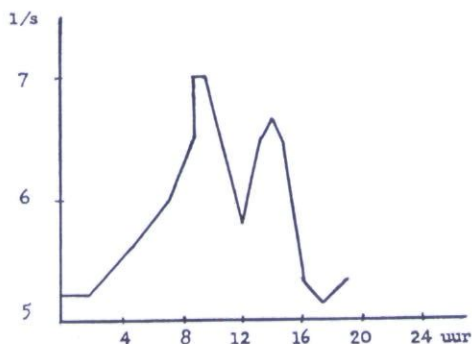


Fig. 2.

The pneumotachographically recorded velocity of expiratory air in our cases was only measured when the patient was exhaling as fast and deep as possible; he first had to take a deep inspiration. The noted values are smaller in cases of bronchostenosis, rigidity of the thoracic wall, weakness of the respiratory muscles and emphysema.

When we repeat the pneumotachographic examination in a patient with asthmatic bronchitis, the 3 circumstances last mentioned always remain the same. So the results noted only depend upon his degree of bronchostenosis.

In normal persons, we found a pneumotachographically recorded velocity of expiratory air of 7 liters to the minute and sometimes more (up to 12 liters). In asthmatic patients this number was smaller: 2-4 liters, or in severe cases even half a liter to the second.

Wysz with this same method of investigation found a peculiar rhythm of the bronchospasm in cases of asthma (see figure 2). This condition was not found in healthy people. Perhaps the fluctuations were too small to be shown. We could confirm these figures.

Recently, *Wysz* and *Hadorn* (6) communicated their results of

pneumotachographic determinations of the broncholytic activity of several drugs in cases of asthma. They pointed out that it is important to undertake these investigations in the evening hours, when bronchospasm is distinct. They could confirm the experiences of other investigators and found the broncholytic effect of several drugs much more pronounced when administered as an aerosol than when given subcutaneously or orally. The effect of adrenalin 0.5 % was regarded as good. The inhalation of higher concentrations such as 2½ or 5 % gave no better result. They arranged a number of drugs in order of broncholytic effect: ephetonin 5 %, adrenalin 0.5 %, ephetonin 20 %, aleudrin 1 %, aleudrin 10 %, adrenalin 5 %.

We object to their investigators as to the light degree of bronchospasm encountered in their patients at the beginning of their experiments. In this way it is difficult to estimate the activity of the various drugs. Moreover, too few patients were tested to obtain reliable results.

Our own experiences with pneumotachography refer to its use in lung-function studies as well as its use in the estimation of the activity of bronchodilator drugs, administered as an aerosol.

It appeared to us that there is a distinct connection between the maximal breathing capacity and the amount of air expired in the first second (V_1), on the one hand, and the velocity of the expiratory air measured by pneumotachography, on the other hand. This similarity however was not so striking that a special value of the pneumotachograph could lead us to draw any conclusions as to a special value of the maximal breathing capacity. The most striking similarity was found with the value K of the hyperbole of *Windemuller*.

We now want to inform you about our results, obtained in an investigation of the activity of bronchodilator drugs.

In 30 cases of severe asthmatic bronchitis, that were first treated in vain orally with the most usual drugs (jod. kal., ephetonin, theophyllin, aminophyllin etc.) for several months, we investigated in the evening hours by pneumotachography the maximal velocity of the expiratory air. This was done when the patient had rested for half an hour and when he had been treated with an aerosol for 15 minutes. Thereupon the investigation was repeated every 20 minutes during the following 2 hours. With respect to their bronchodilator action, the following drugs were investigated:

water
theophyllin 2 %
aminophyllin 2 %

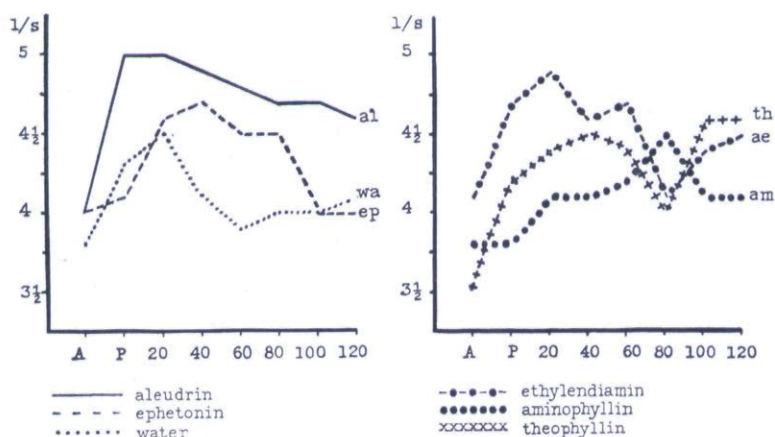


Fig. 3.

ethylendiamin 2 %
 ephetonin 3 % + sulfas atropini 0.03 %
 aleudrin (neo-epinin) 0.3 %.

Hypertension and heart diseases were excluded from this series as ephetonin is contra-indicated in these patients.

We observed the following results:

Water: Sometimes it had a bronchodilator effect; in 5 of our 30 patients we saw some increase in the expiratory air velocity. However in these cases the effect of an aerosol of aminophyllin, theophyllin or ethylendiamin was almost equal. Only ephetonin and aleudrin had a pronounced and better effect (see figure 3).

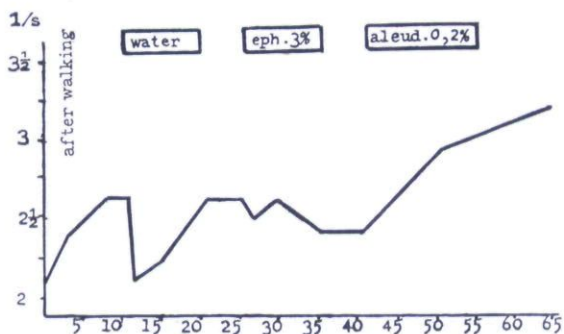


Fig. 4.

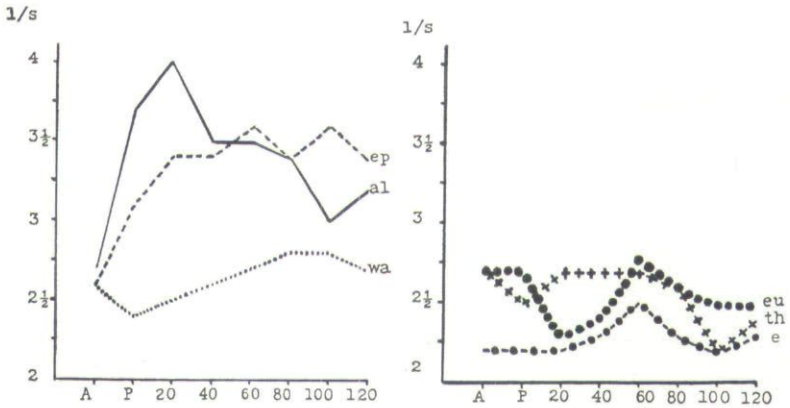


Fig. 5.

In a small number of patients an aerosol of water resulted in an increased bronchoconstriction (see figure 4).

Theophyllin, aminophyllin and ethylendiamin generally had little effect or none at all (see figure 5).

Theophyllin administered as an aerosol twice resulted in an increase of 1 to $1\frac{1}{2}$ liter to the second, six times of $\frac{1}{2}$ to 1 liter to the second, and four times a dubious increase; in the other 18 persons investigated, the bronchodilator effect was entirely absent.

Aminophyllin administered as an aerosol twice resulted in an effect of 1 to $1\frac{1}{2}$ liters to the second, four times $\frac{1}{2}$ to 1 l/sec. and once a doubtful effect. In the other 23 cases no effect could be observed.

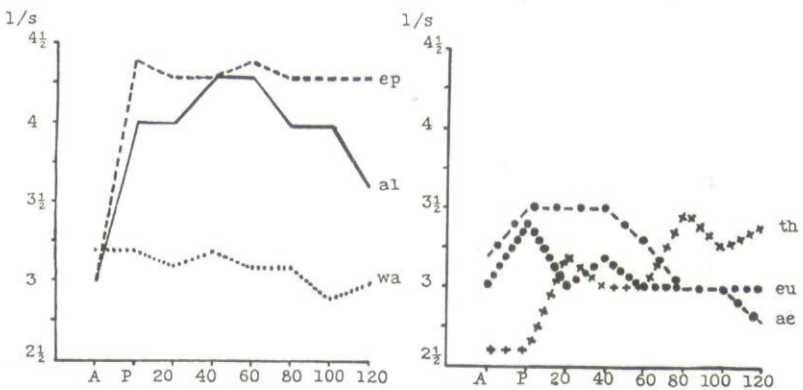


Fig. 6.

Ethylendiamin in two instances resulted in an increase of $\frac{1}{2}$ to 1 l/sec. In the other 28 patients no bronchodilator effect was observed.

Ephetonin 3 % + sulfat atropini 0.03 %. Since 1949 we have used this drugmixture as an aerosol and have noticed good results in patients with chronic asthmatic bronchitis. Yet, we were surprised to perceive now that this mixture had such a pronounced bronchodilator effect. As compared with aleudrin this action was sometimes more distinct, as can be seen in the following list, in which only the difference between the two investigations have been recorded.

Patient	Ephetonin+atropin	Aleudrin
1. male 21 years	2.0	2.0 l/sec.
2. " 41 "	1.5	1.5 "
3. female 52 "	1.4	1.3 "
4. male 61 "	1.0	1.0 "
5. female 23 "	0.6	0.6 "
6. male 54 "	0.5	0.5 "
7. female 20 "	0.4	0.3 "
8. male 45 "	1.5	0.4 "
9. " 55 "	1.1	0.2 "
10. " 37 "	1.1	0.3 "
11. " 52 "	1.5	1.0 "
12. " 48 "	1.4	1.0 "
13. " 64 "	1.3	1.0 "
14. " 58 "	1.1	0.8 "
15. " 52 "	0.9	0.6 "
16. female 37 "	1.2	1.0 "
17. male 46 "	0.6	1.4 "
18. female 48 "	0.8	1.4 "
19. male 64 "	0.3	0.9 "
20. " 59 "	0.1	0.6 "
21. female 38 "	1.2	1.7 "
22. male 72 "	0.6	1.0 "
23. female 51 "	1.2	1.5 "
24. male 46 "	1.2	1.5 "
25. female 56 "	1.0	1.3 "
26. male 63 "	0.7	1.0 "
27. female 51 "	0.3	0.6 "
28. female 39 "	0.0	0.0 "
29. male 28 "	0.0	0.0 "
30. " 20 "	0.0	0.0 "

From these tables we can extract the following groups:

In 7 patients the bronchodilator effect of aleudrin was equal to mixture ephetonin-atropin (see figure 6).

In 9 patients the bronchodilator effect of aleudrin was worse than mixture ephetonin-atropin (see figure 7).

In 11 patients the bronchodilator effect of aleudrin was better than of the mixture ephetonin-atropin (see figure 8).

In 3 patients no effect could be seen in any of them.

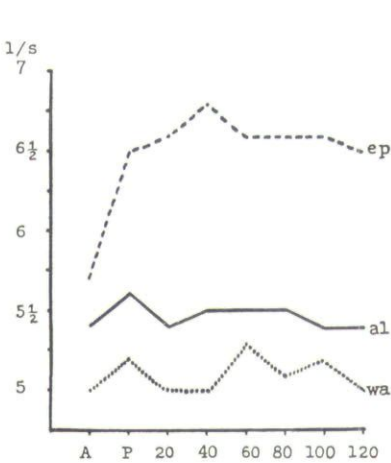


Fig. 7.

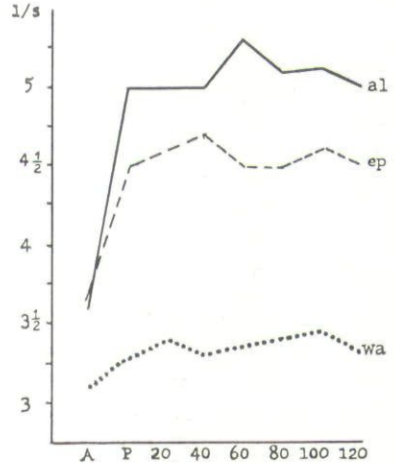


Fig. 8.

From the pharmacological literature we can see that aleudrin has the most active bronchodilator effect on bronchial muscles (7). The latter is almost 1700 times as active as ephetonin. How can it be possible that we found a good result with an aerosol of aleudrin in only 18 of our 30 cases of chronic asthmatic bronchitis? The aerosol therapy with the mixture of ephetonin and atropin had a good effect in 16 of our cases; 9 times it was even much better than that of aleudrin.

Doubtless this bad result of aleudrin can only be explained by the nature of our patients. For they had all an asthmatic bronchitis, that lasted many years and had been treated with oral drugs for several months without any notable effect. Besides it is of importance to remember that 21 of our 30 patients with this intractable asthmatic bronchitis were older than 40 years.

Already in the year 1949 André (8) pointed to the regular occurrence of two types of chronic asthmatic bronchitis. In the first type,

we find the stenosis of the airways caused by a bronchiolar spasm. In the second type, this spasm is but small; but the stenosis is here caused by mucus in the air passages. Between both types of asthmatic bronchitis all sorts of transitions can be seen and no doubt these are in the majority, yet in a small number of cases these pure types occur. Prognosis is poor in the secretory type. In cases of status asthmaticus that run a fatal course, this secretory type is found in the majority of cases.

André showed us that both these types of asthmatic bronchitis can be distinguished in an easy manner by giving the patient an aerosol of aleudrin. When a fast and considerable improvement is seen following the inhalation of aleudrin, one has to do with the spastic type of asthmatic bronchitis. When the administration of such an aerosol has no effect, one has to do with the secretory type. He especially saw this last type occur after the age of forty.

Dautrebande (9) showed us good results of an aerosol of atropin in cases of the secretory type of bronchitis. Only after the atropin having checked the production of the tough mucus, so that the air passages were large again, he administered aleudrin in order to eliminate the spastic factor.

In several cases of asthmatic bronchitis of the secretory type we also saw good results of an aerosol of sulfas atropini 0.05 %. An example can be seen in figure 9. Indeed the administration of aleudrin afterwards, sometimes proved to be necessary to eliminate light spastic factors in these cases.

We now understand why we found such a bad response in 9 of our 30 cases of asthmatic bronchitis by giving them an aerosol of aleudrin. The results of an aerosol of ephetonin-atropin were much better in these case all these patients had the secretory type of chronic asthmatic bronchitis.

In order to prove this we treated them with an aerosol of pure crystalline *trypsin* (trypure Novo¹). From our own experience we knew that it was better to add some aleudrin to it in order to avoid bronchial spasm.

In 7 of the 9 patients suffering from asthmatic bronchitis of the secretory type that were thus treated we could remove the tough mucus from the air passages by giving them an aerosol therapy with the mixture of trypsin and 0.3 % aleudrin. In all these cases an aerosol of

¹ We wish to express our thanks to NOVO Ltd., Copenhagen, for placing this drug at our disposal.

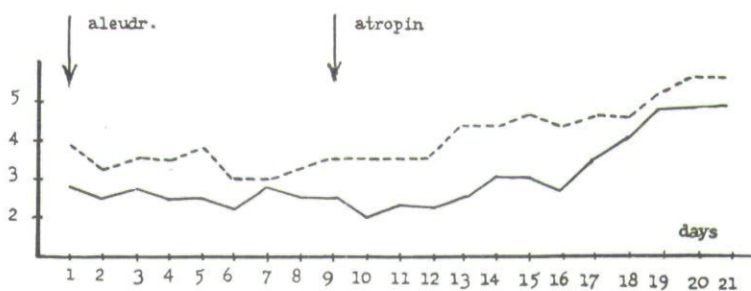


Fig. 9.

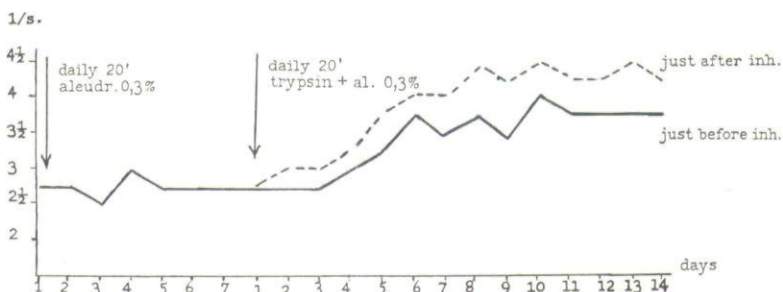


Fig. 10.

0.3 % aleudrin alone produced no result, even when it was continued daily for 20 minutes for a fortnight.

Already in the year 1952, the first reports of trypsin medication were published (10). Several authors described that as a result of trypsin aerosol therapy sputum production became more abundant and also that its constitution became thinner. The viscosity of the sputum decreased (11).

Trypsin is the well known proteolytic pancreatic ferment. Proteins, such as fibrin and mucin, are destroyed by it, but living tissues are not affected. The Armour factories in Chicago and the Novo factories in Copenhagen placed this drug on the market, nearly at the same time in the year 1952. In America the investigators all noticed the same side-effects, which we could also observe: hoarseness, fever, shortness of breath. However when giving anti-histaminic preparations these symptoms might be anticipated.

The trypsin preparation of the Novo factories is a purer product. It did not produce any side-effects in our patients. It is a white crystalline powder that can easily be dissolved in water, but is not

constant in solution. We experienced that its proteolytic action is still present on the following day, provided that it is kept in an ice-box.

In medical practice trypsin proves to be a powerful drug in cleaning surfaces of wound. It can also be administered by intrapleural route in order to obtain lysis of fibrin and blood clots in cases of hemothorax and empyema (12, 13). Finally, it can be given by intrabronchial route in order to obtain lysis of the tough mucus in the air-passages. The benefits of this last method of administration occur when giving aerosol therapy in patients with post-operative atelectasis (14), asthma or bronchitis and bronchiectasis, whether it is combined with emphysema or not (15, 16, 17).

In order to show you the mucolytic effect of trypure we kept some mucopurulent sputum at room temperature for two hours with the following diluted trypsin solutions: 0; 0.03 mg%; 0.3 mg%; 1 mg%. We saw the digestion of the sputum, so that the detritus is sinking to the bottom.

We always used the trypure dissolved in a 0.3 % solution of aleudrin. The first day, one vial of 50 mg trypure was dissolved in 30 cc of aleudrin, the second day again it was dissolved in 30 cc, the next two days in 15 cc and later on always in 10 cc. The aerosol therapy was administered daily by policlinic inhalations over a period of two weeks.

We saw a good effect in cases of status asthmaticus and in most cases of chronic asthmatic bronchitis of the secretory type.

A spastic bronchitis often sets in in cases of bronchiectasis. So in several cases an aerosol therapy with aleudrin alone can lead to a remarkable decrease in sputum production, but when adding trypsin the sputum becomes less tough and the condition of the patient is further improved. The character of the accompanying bronchitis is here of decisive importance; so we must find out whether it is of the spastic type or of the secretory type.

As both types of bronchitis often occur combined in patients with bronchiectasis or asthmatic bronchitis we see the best results when first giving the patients an aerosol medication of aleudrin 0.3 %. When no satisfactory results are obtained, the patient is given an aerosol of a mixture of aleudrin 0.3 %, sulfas atropini 0.05 % and trypsin in the doses above mentioned.

SUMMARY

A comparative examination of bronchodilator activity was undertaken with several drugs: water, theophyllin 2 %, aminophyllin 2 %,

ethylendiamin 2 %, ephetonin 3 % + sulfas atropini 0.03 %, aleudrin 0.3 %. The results with the ephetonin-atropin solution were surprisingly good. The investigation was undertaken with pneumotachography in 30 patients with chronic asthmatic bronchitis, who had already been treated with numerous oral drugs in vain. Two types of asthmatic bronchitis were seen: the spastic and the secretory type. In this last type, good results were obtained with trypsin as an aerosol. The results were still better with an aerosol of a mixture of aleudrin 0.3 %, sulfas atropini 0.05 % and trypsin.

LITERATURE

1. *Windemuller, P. J.*: Thesis, Utrecht, 1951.
2. *Fleisch, A.*: Pflügers Arch. 209, 713, 1925.
3. *Hadorn, W.*: Schw. Med. Wschr. 946, 1942.
4. *Wysz, F.*: Helv. med. acta 17, 516, 1950.
5. *Roth, P.*: Thesis, Bern, 1950.
6. *Wysz, F. & Hadorn, W.*: Progress in Allergy 3, 920, 1952.
7. *Hawkins, D. F. & Schild, H. O.*: Brit. J. pharm. 6, 682, 1951.
8. *André, M. J.*: Presse méd. 15 Jan. 1949, 73.
9. *Dautrebande, L.*: L'aérosologie, J. B. Baillière et fils, édit. 1951.
10. *Limber, C. R., Reiser, H. G., Roettig, L. C. & Curis, G. M.*: J.A.M.A. 149, 816, 1952.
11. *Yates, J. L. & Goodrich, B. E.*: Dis. Chest 24, 320, 1953.
12. *Dellaunoy, E. & Ribet, M.*: Presse méd. 61, 97, 1953.
13. *Miller, J. M., White, B. H. & Ginsberg, M.*: Dis. Chest 26, 166, 1954.
14. *Crawen, J. F.*: J. pediatr. 42, 228, 1953.
15. *Biron, A. & Choay, L.*: Presse méd. 62, 719, 1954.
16. *Unger, L. & Unger, A. H.*: J.A.M.A. 152, 1109, 1953.
17. *Farber, S. M. c.s.*: J. thorac. surg. 27, 45, 1954.

TURPENTINE ECZEMA

by W. G. VAN KETEL (Amsterdam)

(Will be published in extenso elsewhere.)

SOME THERAPEUTICS IN BRONCHIAL ASTHMA

by Mrs. BOOY-NOORD (Groningen)

SOME CASES OF ALLERGIC ABDOMINAL DISEASES. N.T.v.G.

by W. J. F. VAN DER BIJL (Amsterdam)

BRONCHIAL ASTHMA AND HYPERTENSION

by W. J. QUARLES VAN UFFORD, Utrecht

In discussing this subject I should like you to consider the 5 following items:

1. hypertension and hypotension as allergic reactions.
2. variations in blood pressure during attacks of asthma.
3. asthma and hypertension as unrelated conditions.
4. asthma due to hypertension.
5. asthma associated with hypertension.

Sub. 1. A lowered blood pressure, associated with symptoms of fatigue, asthenia, apathy and aversion to work, is frequently observed in allergic diseases.

As a result of the difficulties involved in identifying the cause of hypertension the question has been repeatedly raised whether hypertension should not be regarded as an allergic disease in some cases.

Funck assumed essential hypertension to be due to a hypersensitiveness to substances produced by bacteria or protein.

Having ingested animal proteins, Bienstock observed a transient rise of his own blood pressure.

Waldbott described food allergies, e.g. to fish, associated with hypertension, which also diminished when the allergens had been determined and eliminated. Vaughan and Sullivan, in reporting 24 cases of food allergy and hypertension, Liston, reporting 15 cases (including one of pork allergy), Gay, reporting 20 cases, Morgenthal, Abderhalden and Feinberg draw attention to the fact that the possibility of hypersensitiveness should be borne in mind in cases of hypertension. Kahn reports 4 cases of asthma and hypertension, in which treatment with adrenaline resulted in a decrease of the dyspnoea and the blood pressure.

Sub. 2. The variations in blood pressure during attacks of asthma have been studied.

Tuft and Alexander observed a fall, Cooke, Urbach and Gottlieb reporting rises in blood pressure. Osgood has drawn attention to the fact that the *blood pressure* varies with the respiration. He claims that the blood pressure attains its maximum during the expiratory phase. This problem had a special bearing on treatment with adrenaline, as there was some fear with regard to the effects of adrenaline in asthmatic patients with hypertension. Others, however, have claimed that adrenaline definitely has no adverse effect on the blood pressure in patients with asthma, but rather the reverse.

Cooke has drawn attention to the fact that patients with hypertension may show an asthmatic dyspnoea, especially when they have had asthma previously. Unger observed hypertension in 20 % of his patients with asthma. He stresses the worse prognosis *ad vitam*. Hansen also regards hypertension as a severe complication, as it results in increased strain on the heart. Sterling defines hypertension as one of the complications of emphysema in elderly subjects. Salén draws attention to the use of treatment with theobromine compounds in asthma in view of the favourable effect on the circulatory system, especially in those cases in which hypertension has resulted in vascular changes.

De Langen, Gollwitz, Meier and Gilhaus report a fall in blood pressure obtained by treatment with histamine. Pal also draws attention to the hypotensive action of a number of proteinogenous amines from the histidine-histamine and the lecithin-choline series.

Hagen, Bettmann and al. observed abnormally marked changes in the vascular system (paralysis, spasms) following thunderstorms and sudden changes of weather. According to Petersen and Vaughan meteorological changes, and especially the advent of polar air, markedly affect vasoconstriction and vasodilatation, as manifesting themselves in variations in blood pressure. (This is also claimed to occur fairly often in cases of asthma).

Howe observed that periods of peripheral vasodilatation (fall of the diastolic pressure) coincided with an increased response to tuberculin.

We shall now report some personal cases.

Sub. 3. Asthma and hypertension as unrelated conditions. One case (treated by van Melle) was that of a 46-year-old man, who developed a sense of suffocation, especially following exercise, shortness of breath and a sense of oppression early in 1946. No coughing or expectoration. Frequent headaches. A hypertension had been found as early as 1943, for which the patient was ordered to take a saltfree diet and to rest in bed. In addition, nasal polyps were detected. The father, an uncle and an aunt (both on the father's side) died from apoplexy, a brother is affected with hypertension. The blood pressure was found to be 220/140 (180/130 during sleep induced by veronal). Splanchnicotomy was performed. Some weeks later the patient was discharged from the hospital with a blood pressure of 155/120. Wheezing occurred shortly afterwards (the blood pressure rose to 180/120) and one year later the patient had to be hospitalized again for nocturnal dyspnoea as-

sociated with an asthma-like bronchitis. Treatment with ephedrine afforded relief. Eosinophilia 7 %. For a year he was in and out of the hospital for attacks of asthma. A stay in Switzerland resulted in some improvement. On returning home, he was immediately subject to severe attacks. It was at that time that I first saw the patient. Skin tests were positive for some inhalation and food allergens. Pyretotherapy with a sulphur compound resulted in loss of consciousness, but subsequently the symptoms disappeared for some time. Later, treatment was continued with pyriferylene. The dyspnoea diminished. Some time after, the patient was transferred to a rest home, where he soon died. This was not a case of congestive bronchitis. Possibly there were two different clinical pictures, that of sympatheticotonia (with hypertension) and that of vagotonia (one of the symptoms of which also is bronchial asthma according to Bing). This might also explain the fact that a number of asthmatic patients with hypertension show an increased dyspnoea when treatment with Rauwolfia drugs is initiated.

Sub. 4. Asthma due to hypertension.

In July 1953 a 70-year-old lady arrived at my out-patient department, stating that she had been subject to increasing attacks of dyspnoea and coughing for the past 3 months, without expectoration or wheezing. The patient had had a chronic bronchitis 3 months previously. The blood pressure was 170/90, ESR 17-41, eosinophilia 9 %. Skin tests were positive for dust, pulses, beef, spinach, chicory and onions. The pulse rate was 112, the pulse being irregular.

X-ray examination: pulmonary outlines too sharp, especially on the right side, the diaphragm does not move freely.

Circumference of chest: 84-87. Auscultation revealed shallow breathing and wheezing, with a prolonged expiratory phase. The patient was hospitalized and treated with a salt-free diet, antibiotics and digitalis. This resulted in a more equal and less irregular pulse. The blood pressure fell to 130/90. The eosinophilia decreased to 5. or under. The patient was still without symptoms 15 months later. Mrs. v.d.P. (aged 43) having been subject to 4-5 attacks of dyspnoea, suddenly and after exercise, every year for the past 10 years after she had contracted a bronchitis by falling into the water. Wheezing, not much coughing, no expectoration. A sister was affected with bronchial asthma. ESR 10-30, blood pressure 180/115, occasionally rising to over 200. Eosinophilia 0-5. Auscultation of the lungs: wheezing, occasional rhonchi. Skin tests positive for cats, dust, eggs, milk and tomatoes. The ECG showed only slight changes. X-raying revealed

no changes in the heart and lungs. The patient was treated with a salt-free diet, bed rest and prominal; later, when the blood pressure failed to show a sufficient decrease, she was also given "wolfaserpol". In addition, a treatment with autovaccine was initiated. Since then the symptoms have decreased considerably.

Sub. 5. In May 1948 Mrs. C.v.W. (aged 60) came to my out-patient department, stating that for some years past she had been subject to fits of coughing and attacks of dyspnoea, especially after exercise and coughing. Circumference of chest 78-80, ESR 12-30, blood pressure 150/105, eosinophilia 10-15. X-ray examination: no changes. Examination of the lungs revealed wheezing and a prolonged expiratory phase. Skin tests positive for dust, straw and flour. Treatment with an autovaccine resulted in a good general condition. A few sporadic attacks of dyspnoea were effectively controlled by treatment with euphylline and powdered ephedrine. A hypertension of 230/120 was observed in 1950. The ECG showed evidence of left ventricular preponderance. A salt-free diet and bed rest resulted in a fall in blood pressure. During the last months—respiration continued to be good—the blood pressure has increased again. At the time of writing she is being treated with "wolfaserpol". There was never any relationship between rises in blood pressure and an increased dyspnoea. The dyspnoea only showed an increase during the first weeks of treatment with "wolfaserpol".

Nevertheless, the blood pressure is followed closely. As a lowered blood pressure is the change most frequently observed, we are inclined to consider a blood pressure, normally regarded as only slightly increased, to be considerably increased in allergic patients. Accordingly they are treated as such. Like Unger and Hansen, I have also gained the impression that the prognosis *ad vitam* is worse in patients with asthma and hypertension than in others. I was called into consult in the case of a 48-year-old lady, who had developed a severe bronchial asthma for the past 3 years, following a persistent vasomotor rhinitis. The history of the patient showed that she had also had attacks of angioneurotic oedema. The family history showed no evidence of asthma. She had previously been placed on diet, which treatment had not been altogether very successful. Circumference of chest 95-99, ESR 20-39, eosinophilia 9 %, blood pressure 190/110. The ECG showed no changes. Skin tests markedly positive for house dust. House dust treatment resulted in a considerable improvement. The patient recovered her zest in life and then started to keep a less rigidly salt-free

diet and a less strict bed rest, chiefly because the people surrounding her did not really regard the blood pressure, which had fallen to 160, as dangerous. One year later the patient suddenly died, however, the heart having failed after all.

It is cases of this type that have induced me to discuss this subject and to put the question whether one is not justified in regarding asthmatic patients with chronic hypertension (even when it appears to be only very slight) with scepticism. Apparently this association has a strongly adverse effect on the heart.

W. J. Quarles van Ufford,
Secretary.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.