Concluding Remarks

In conclusion I should just like to say a word regarding those who do not require to consider every penny spent on food. Faulty dieting is not uncommon among this class, where appetite is, as a rule, the sole dictator of intake. It is true that certain workers have stressed following the dictates of appetite, but it is very difficult to say whether this is always a sound line or no in the human being. There is ample evidence that it is an effective guide in the case of certain animals like pigs, dogs, and rats, which are not pampered and are given a free choice in the selection of their food. There is no question about the fact that apparently perfectly normal human beings exhibit wide variances in their food preferences, based often, I believe, on real but probably more often on imaginary needs. Again I emphasize the point that in this question of food the problem is frequently as much psychological as physiological. "Better a dinner of herbs, where love is, than a stalled ox and hatred therewith" is very sound doctrine. The great danger is that people develop a pathological interest in food, that they become food-conscious due to the superfluity of ill-advised chit-chat concerning the virtues or evils of this or that article of diet. It is infinitely more profitable to follow the advice,

"Eat all kind Nature doth bestow;
It will amalgamate below
If the mind says it shall be so.
But if you once begin to doubt
The gastric juice will find it out."

THE "DISPOSITION" AND THE SPECIFIC ALLERGEN IN ASTHMA, HAY FEVER, AND OTHER ALLERGIC CONDITIONS

BY

E. M. FRAENKEL, M.D.

The phrase "allergic disease" means no more as a diagnosis than the terms "infectious disease" and "metabolic disease." Three alterations in the normal behaviour of the tissues are considered to be characteristic of allergic conditions and reactions. The most striking of these is the constriction of the smooth muscles, such as takes place in the bronchial spasm of asthma, in the spasm of the bowel in spastic colitis, or in the vascular spasm that is presumed to take place in migraine. The second alteration is a localized exudative increase in the water content of certain tissues, such as occurs in the skin in Quincke's oedema and in the mucous membranes in rhinitis and other catarrhal conditions. The third alteration that is often present is a generalized or localized increase in the eosinophils. In most cases a combination of all three of these conditions is characteristic.

The Allergic Reaction

This type of so-called "allergic reaction," particularly the constriction of the smooth muscle fibres, is an effect that can be produced by irritation of the parasympathetic nervous system. It is therefore conceivable that anything and everything causing such an irritation would result in the same complex of symptoms and that everything capable of counteracting this irritation could be used as a therapeutic or prophylactic agent. The parasympathetic irritation might be due to a reflex action from a special

area. An abnormally high irritability of an area, as in the conjunctivae and the nasal, bronchial, and intestinal mucous membranes, might therefore be responsible for the onset of reactions induced by irritants harmless to less sensitive parts or persons. On the other hand, it shows that the hypersensitivity towards irritation at one spot does not usually mean that there exists a general hypersensitivity of all tissues of the body, and it is in this way that the localization of the irritability may be produced.

The irritability of the parasympathetic nervous system, however, depends on such general metabolic factors as the balance of potassium and calcium salts in the mineral content of the tissues. The calcium acts as a stabilizing factor; in a similar way other metabolic factors may act as sympathetic or parasympathetic irritants, and others may prevent this irritation. For example, such endocrine products as pituitrin and adrenaline counteract the irritation of the parasympathetic by counter-irritation of the sympathetic, whereas a drug like atropine protects the parasympathetic from irritation. It may thus be understood that the constitutional behaviour of different types of patients at different periods of life—as at puberty and during the menopause—or while subject to endocrine disturbance, can so alter their irritability that they become hypersensitive towards otherwise innocuous irritants. The regulation of the sympathetic nervous system by the higher centres and by psychic factors may work in both directions, causing either an increase or a decrease in the irritability. Cures brought about by suggestion therapy cannot therefore be used as proof of the psychological origin of the irritability.

Disposition Towards Allergic Irritation

Irritability of the sympathetic nervous system cannot be neglected in the investigation and treatment of allergic patients. It is the variation in the conditions mentioned above that we may call the disposition of the patient towards specific allergens. A change in both local and general irritability may be brought about by a variety of factors. To these is added the factor of the external irritant, the so-called allergen. A number of allergens are so powerful that they produce an allergic condition in all persons exposed to their action. These are followed by a number ranging in potency down to those so weak that they give rise to symptoms in only a few particularly susceptible persons. Hay-fever pollen, for example, affects about 1 per cent. of the population of large towns, whereas it has been found in Switzerland that the country people are affected only to the extent of about 0.2 per cent. of the population. This shows clearly that the same allergen has a different effect upon a population under different conditions, and that the disposition plays a definite part in allergic diseases.

The mechanism of an allergic reaction is probably similar to that of an anaphylactic shock or to that of parasympathetic irritation in general. It has been shown by Dale and others that both anaphylactic shock and nervous irritation are either followed or caused by the formation of acetylcholine in the tissues, acting in a similar way to histamine in causing contraction of the smooth muscles. It is not yet quite clear whether these or similar compounds can be split off from the supposed allergen, or whether, in the case of allergic reactions, they are produced by the cells of the subject under the influence of a specific parasympathetic irritation.

Theoretically any type of irritation, physical or chemical, acting in conjunction with the factors described above, could give rise to any one of the reactions known as allergic. In point of fact the well-defined allergens

are usually thought to be of the nature of proteins, and with such chemical substances as "ursol," salicylic acid, and pyramidon it is believed that a compound of these and of the proteins of the body has been formed and endowed with allergic properties. The mechanism of such a reaction will be understood when I refer to Landsteiner's allergens, where a compound of such chemical substances as benzyl chloride with various proteins was effected. These compounds produced group-specific antibodies and reactions towards the chemical substance in question, and not towards the protein.

The Specific Allergen

The specific allergen is well known in hay fever and the asthma occurring in furriers, as well as in certain other cases. It is also recognized in the urticaria produced by foodstuffs—for example, strawberries and crayfish—or by primula. These examples show that there exists a very wide range of substances that can act as allergens. The allergen can enter the body by means of inhalation, as in hay fever and in furrier's asthma. Such air-borne allergens are a very common cause of allergic conditions. The allergen may enter the body in the form of a food-stuff in urticaria and in the eczema of babies who are given unsuitable food. Foodstuffs may also provoke an attack of asthma or of mucous colitis.

The entrance of allergens through the skin is known to occur in many eczemas of occupational origin, and an example of the subcutaneous mode of entrance is afforded by the "serum sickness" that sometimes ensues from treatment with horse serum. These examples demonstrate another important fact—namely, that the site of entrance of the allergen is not identical with the organ in which the symptoms are manifested. A parenteral injection may give rise in the skin to urticaria or Quincke's oedema, in the bowels to colitis, or in the respiratory tract to asthma or to rhinitis; the same is true of other modes of entrance of the allergen.

Experience has shown that an allergic reaction is from the beginning as specific as any other immunity reaction. The allergy usually begins with a hypersensitivity towards one or two well-defined allergens (monovalency). Gradually, however, if the condition does not receive proper treatment, the body becomes more and more sensitive towards other allergens (polyvalency). It is to be recommended that in these cases the threshold of sensitivity be raised rather than an attempt be made to remove any allergen in particular. This can, of course, be accomplished by the treatment of constitutional factors as well as by desensitization.

In other cases, however, the role of the specific allergen is predominant, and the detection of this and the subsequent protection from or immunization against it constitute the only satisfactory method of treatment. There are allergens which, in a similar way to a universally pathogenic micro-organism, result in allergic symptoms in all who come under their influence. An example of this was afforded by Frugoni and Ancona, who found that peasants suffered from asthma after working in fields infected with a certain species of tinea, and there is also the example of the purified allergen produced by Bloch and his collaborators from primula which provoked urticaria in everybody who received an injection of it.

Many attempts have been made to isolate the responsible chemical compounds from the various allergens. It is, for instance, considered probable that in hay fever carbohydrates of a similar structure to the antigenic carbohydrates existing in bacteria are responsible. We have,

on the other hand, some experimental evidence, obtained from the use of masks equipped with filtration apparatus, that in epidermal allergens such as feathers it is probable that they are more of the nature of an essential oil or of a protein in such a fine state of subdivision that it is dissolved with facility in the microdroplets of water present in the atmosphere.

TWO EXAMPLES

The specificity of the allergen may be illustrated by two cases.

A young lady, recently married, had before marriage suffered from asthma when living in her parents' house, but had been free when living in a boarding house in town. After her marriage she invariably suffered from attacks of asthma at night. As an extract of feathers produced a positive skin reaction she was sent to a sanatorium, where she was advised to sleep on bedding free from feathers, and here she was entirely free from any symptoms. Subsequently, while travelling, she often slept on feather beds in hotels, but never suffered from any attacks. On her return home she slept once more on her own feather bed, and the asthma immediately returned. Extracts from the feathers in her bedding gave a very strong skin reaction, and she admitted that her bedding had been brought from her parents' home. On my advice she disposed of the bedding in question, not without first getting a violent attack after beating and cleaning it. It is probable that some contaminating substance was present in these particular feathers, and it was this substance that produced the marked specificity.

Another lady suffered from severe attacks in Königsberg, but was completely free in Berlin. It was possible to show that the inhalation of the street dust of Königsberg was responsible for the asthma, and positive skin tests were obtained with extracts of this dust, whereas no such results were obtained with the street dust from Berlin.

These two examples show that such substances as dust and feathers are in reality very complicated mixtures of a large number of individual substances, and are not comparable with a specific allergen from a definite mould, bacterium, or grass pollen.

Diagnostic Methods

The only real proof that a particular allergen causes the allergic condition is the production of this in the patient after exposure to the allergen and the cure of the condition subsequent to its removal. Such an experiment is, of course, disagreeable for the patient, and, although the attack can be controlled by the judicious use of adrenaline, involves a certain degree of risk. Nevertheless the "exposure test" and the "removal test" are the diagnostic aids that finally decide the specificity of the causal allergen. The first may be used with appropriate caution in a clinical institution, where every aid is at hand should it be necessary to deal with an unwanted reaction. The second may be safely used in private practice. In private practice, however, the most important diagnostic features are the history of the patient and of his family regarding allergic complaints and their relation to factors in their surroundings, both professional and domestic. These diagnostic features also include an eosinophilia of the blood and of the excreta, including both sputum and stools, and the production of skin reactions with extracts of alleged allergens.

With the "exposure test" I have been able to determine the exact mode of entrance of the air-borne allergen by means of a mask that afforded protection to the conjunctivae, the nasal mucous membrane, or the mouth, or to any combination of these. It was already known that the protection of the conjunctivae by goggles would prevent the onset of rhinitis and asthma in some hay-fever patients.

Illustrative Cases

In one of my patients who had a hypersensitivity towards dog's hair a mask protecting the conjunctivae and nose alone, with the mouth unprotected, prevented the onset of an attack of asthma. I was able to prove in the same case that the protection afforded by filtration apparatus and a mask was only of use so long as the filter remained in operation. As soon as the filter was replaced by a dummy, exposure to dog's hair was followed by an immediate attack of asthma. This result being obtained in a patient who believed herself to be protected is a proof that the asthma was actually produced by the allergen and that no protection was afforded by a mere psychological factor. There are, however, only a small number of patients in whom the intake of an allergen is immediately followed by the production of obvious allergic symptoms.

Another patient, who had observed that his attacks always occurred after eating a certain variety of peas, had an attack in hospital after eating such peas, and at the same time gave a tremendous skin reaction on being injected with a small quantity of pea extract. Such specific cases are rare but characteristic, and they afford a reliable proof of the specific role of the allergen.

In another patient the history suggested that the onset of his attacks dated from the time he began work as a furrier. The skin tests in the case showed, however, that he had a marked hypersensitivity towards bed feathers, and his condition was immediately cured by removal of feathers from his bedding.

Although the history was misleading in this instance I still believe that in most cases, especially where skin tests give inconclusive results, it is of the greatest importance to employ the history as a guide in the choice of allergens that should be used in testing and for the interpretation of the results. A positive skin test, whether obtained by the cutaneous or intracutaneous method, should exhibit a marked wheal with a surrounding inflammatory zone which may be as large as a halfpenny or even larger, and which may or may not be accompanied by other distant or general allergic symptoms. Where specific reactions are expected, as in hay fever, it is desirable that only the cutaneous method of skin testing should be used in order to avoid disagreeable symptoms.

I have recently shown that the area of a reaction becomes, for the few hours following its appearance, insensitive to the injection of other allergens, but not to that of a solution of peptone. I would hesitate, however, to conclude from these observations that in all these allergens the same substance is responsible for the reaction. This has been said of the hay-fever allergens derived from many types of pollen, and it has for this reason been maintained that it is sufficient to carry out desensitization with only one or, at most, a few pollens, and that this technique gives the same results as the use of individual extracts. My own experience, however, does not support this conclusion, as the following case shows.

A boy, aged 15 years, had suffered from a "status asthmaticus" from 1931 to 1933 in all parts of Europe, both in low-lying country and in the mountains. Skin tests showed him to be hypersensitive towards *Festuca rubra*, *Dactylis glomerata*, *Lolium perenne*, *Cecale cereale*, *Triticum vulgare*, *Trisetum floresce*, *Agrostis canina*, and *Elymus gigantes*. After a course of injections in 1934 he had a few attacks of rhinitis, but no asthma during the hay-fever season of that year. During the next year the three last allergens were found no longer to give skin reactions, and reactions to all the others, except *Festuca rubra* and *Cecale cereale*, were diminished. A fresh course of injections with a new mixture which included Timothy grass (*Phleum pratense*)—although this was negative in skin tests—and *Alopecurus pratensis* was given, and, although 1935 was a particularly bad season for hay-fever sufferers, complete freedom has been enjoyed during the subsequent two years.

Most allergic patients do not show the markedly specific reactions obtained in hay fever, and tend to react with an

assortment of allergens. In such, comparison with a carbol-saline control and the comparison of the various tests, together with the history of the patient, gives a certain guide in the judgement of the tests. But these reactions cannot be considered to be as reliable as the marked reactions mentioned above, and much experience and judgement is necessary for their correct interpretation. It must be remembered that bacterial allergens usually produce reactions after much longer intervals (up to as long as twenty-four hours), which can perhaps be explained as being due to the same mechanism as that responsible for Schwartzmann's phenomenon or to a similar one.

Another specific test that is perhaps too complicated to be employed for general purposes is the Prausnitz-Kuestner reaction, in which the passive transmission of the hypersensitivity from an allergic patient to a normal person is secured by means of an injection of the affected person's blood serum. The hypersensitivity, which is purely local, occurs at the site of the injection after a few hours. In some instances eosinophilia was of use in diagnosis, as in nearly 50 per cent. of the allergic cases there is an eosinophilia of the blood of over 5 per cent., and in one of my asthma cases the eosinophilia was as high as 53 per cent.

Clinical Experience

Up to the present time my experience comprises about 800 allergic cases: 200 of these were observed a few years ago in the Charité Hospital in Berlin, and the remaining 600 in private practice and at certain other hospitals. Most of these cases were asthmatic, but a part of them were cases of hay fever and other allergic diseases, including vasomotor rhinitis, Quincke's oedema, urticaria, migraine, and mucous colitis. In a survey of 522 asthma cases published in 1934 I found allergic symptoms such as an eosinophilia of over 4 per cent. in 221 cases, a family history of allergy in 128, and other allergic symptoms besides asthma in 165. Positive skin tests were obtained in 364. Among the most frequent reactions were those obtained with house dust, which gave 252 positive results. Feather beds and mattresses gave 199 positive results, and eighty-four were obtained with extracts of moulds cultured from allergic surroundings. Bacterial extracts gave positive results in 108 cases, animal fur in forty-two, and other allergens in fifty-five. The majority of cases gave positive results with more than one allergen.

In a previous paper in this *Journal* I discussed the part played by active and inactive tuberculosis in the course of allergic complaints. The role of infections in general and of tuberculosis in particular may be the same as that of any other sensitization, this being produced by the protein of the infecting organism. It may, however, prepare a special part of the body, such as the bronchial mucous membrane, and in tuberculosis the lymphatics and/or the lung tissue, or streptococcal infections the antrum, so that their threshold is lowered towards the entrance of other allergens. On the other hand, I have observed that cases of inactive tuberculous infection have flared up subsequent to or because of desensitization with other allergens. I have also drawn attention to some patients who, with all the symptoms of a true bronchial asthma, prove to have active and open tuberculosis. For this reason it is, in my opinion, essential to examine the sputum for tubercle bacilli and to perform an x-ray examination of the chest as a routine in all asthma cases. In this way diagnostic errors, such as the overlooking of a bronchiectatic condition of the lung, substernal goitre, and other diseases will be avoided. X-ray examination of the nasal sinuses

seems to be of particular importance not only in asthma but more especially in vasomotor rhinitis, and old foci in the antrum may be responsible for the exacerbation of symptoms in operations on the nose.

Treatment and Prophylaxis

It is clear that treatment of allergic conditions, especially of asthma, can and must start from several different aspects. When the specific allergen is the outstanding factor the discovery and removal of it may be followed by complete recovery. It may be very easy in one case and impossible in another.

As the complete range of allergens that are responsible can rarely be discovered in any one case, I make use of those specific allergens that have been detected mixed together with either peptone or small quantities of old tuberculin. Such a mixture is of great use in the treatment of a case in which any doubt remains as to the identity of all the responsible allergens. The treatment begins with a dose of a dilution that has been found, by means of titration in skin tests, to be considerably smaller than the smallest quantity producing a skin reaction. The course of injections, covering a period of ten to twelve weeks, should consist of doses of increasing size, and

until the patient has acquired a high degree of desensitization and consequent immunity.

Summary

The "threshold towards the allergen" varies not only in different persons but in the same person at different periods of life and under different conditions.

Hypersensitivity is consequently a variable factor not only in general but also in particular localized areas.

Thirdly, one has in these conditions to deal with a variety of causes changing the threshold of hypersensitivity. Treatment consists in dealing with septic foci, endocrine and metabolic changes, special physical conditions of the upper respiratory tract and chest wall, and with psychological factors influencing the sympathetic nervous system.

BIBLIOGRAPHY

- Baagoe, K. (1926). *Asthma*, Levin and Munksgaard, Copenhagen.
 Bray, G. W. (1937). *Recent Advances in Allergy*, third edition, Churchill, London.
 Fraenkel, E. M. (1930). *Gesdh. ing.*, 53, 755.
 — (1934). *Schweiz. med. Wschr.*, 64, 1193.
 — (1934). *British Medical Journal*, 2, 513.
 Feinberg, S. M. (1936). *J. Allergy*, 7, 268.
 Hansen, K., Rost, G. A., and Dekker, H. (1930). *Praktikum der Allergischen Krankheiten*, Montana, Horw-Luzern.
 Hamann, M. (1933). *Brauer's Beitr. z. Klin. d. Tuberk.*, 82, 619.
 Gutmann, M. J., et al. (1929). *Pollenallergie*, Gmelin, Munich.
 Kämmerer, H. (1934). *Allerg. Diathese und allerg. Erkrankungen*, Bergmann, Munich.
 Landsteiner, K., and Jacobs, J. (1936). *J. exp. Med.*, 64, 625.

The mask type of allergen-filtration apparatus connected to a high-pressure air supply in horizontal pipe behind chairs.

should not in any way be interrupted. Should, as the doses are increased, a severe reaction occur, the addition of 0.25 c.cm. of adrenaline 1 in 1,000 and/or the reduction of the quantity of the next dose to that of the preceding one will in most cases allow treatment to be continued. I have always tried to begin treatment in allergen-free surroundings. For hay fever it is usual to begin and finish the treatment before the start of the hay-fever season. With house allergens such surroundings may be obtained by means of an allergen-filter apparatus (see figure)—mask, sleeping bag, or cubicle—or by the careful removal of feathers and dust. In instances of food allergy the necessary conditions are obtainable by means of a special diet.

As has been shown before, the majority of cases in adults as well as in children are due to a hypersensitivity towards house allergens. Those next most responsible are the bacterial allergens, and I think it is for this reason that some asthma patients respond to vaccine treatment. The efficacy of such treatment depends very largely on the choice of the correct dose, on the type of bacterial vaccine, and on the time interval and the length of treatment. I prefer to use autogenous bacterial "allergens"

POST-HYSTERECTOMY AND PUERPERAL TETANUS

A STUDY OF THE BACTERIOLOGY OF OBSTETRICAL AND GYNAECOLOGICAL DRESSINGS *

BY

R. J. V. PULVERTAFT, M.D., M.R.C.P.

Reader in Pathology, University of London

The experiments related in this paper were undertaken to discover why a specific case of tetanus developed after hysterectomy, and they were extended to establish the reason why post-operative tetanus is peculiarly related to hysterectomy. It was apparent as a result that the dressings used before the operation contained tetanus spores and other anaerobic spore-bearing pathogens; they were made of "cellulose wadding."

Study of a Case

The clinical features of the case were as follows.

A woman of 51 suffered from intermittent loss of blood per vaginam. At operation an endometrioma of the posterior uterine wall was found attached to the pelvic colon. Total hysterectomy and bilateral salpingo-oophorectomy were performed. Four days later "tonsillitis" developed; and seven days later trismus, with spasms on deglutition. A diagnosis of tetanus was made by two clinicians experienced in the condition. She died twelve days after the operation.

At the post-mortem examination the operation site was found in fair condition, although less union of tissue was present than normal; there was no definite naked-eye sepsis. The spleen was soft and diffused, little evidence of tonsillitis was found, and nothing explaining death.

Material from the wound site was collected, and also a sample of faeces. The tissue cultures yielded morphologically typical tetanus bacilli and spores; the faeces did not. A guinea-pig injected with a mixed culture died with signs of tetanus.

The catgut used at the operation had also been used on the same day on two other cases, which had a normal con-

* From the John Burford Carllill Laboratories, Westminster Hospital Medical School.